PHOTOISOMERIZATION OF BICYCLOOCTANONES IN SOLUTION

SUSAN CLIFT CRITCH

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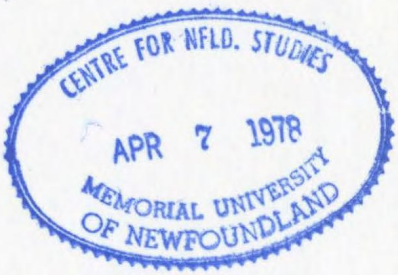

PHOTOISOMERIZATION OF BICYCLOOCTANONES IN SOLUTION

by

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A Thesis submitted in partial fulfillment

of the requirements for the degree of

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ABSTRACT

The photolysis of bicyclo(3.2.1)octan-2-one (XVII), bicyclo(2.2.2)octan-2-one (XXV), and 1,8,8-trimethyl-bicyclo(3.2.1)octan-2-one (homocamphor) (IX) in nucleophilic solvents (methanol, water, cyclohexylamine) is reported. The structures of the products were established by synthesis and comparison with authentic materials, and, in the case of XVII, the two aldehydes (XVIII, XIX) were isolated and the position of the double bond established by nuclear magnetic resonance shift measurements and confirmed by degradation. The spectroscopic properties of the products were recorded.

The photochemical products were predominantly derived from aldehydes and ketenes and the product ratios are tabulated. The results are rationalized in terms of conformational analysis of the diradical intermediates involved. A potential general method of altering the product ratio using cyclohexylamine is described, as are various synthetic approaches to these ketones.

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INTRODUCTION

Interest in the effects of the photolysis of organic compounds has increased dramatically in recent years, stimulated by the application of photochemical methods to the synthesis of natural products and compounds previously difficult to obtain.[1-3] Nevertheless, many facts are still imperfectly understood and the synthetic use of simple photoinduced cleavage reactions has been infrequent due to difficulty in predicting product ratios accurately.

The principal reactions of saturated cyclic ketones on photolysis in solution are α-cleavage, known as the Norrish Type I process, and γ-hydrogen abstraction, the Norrish Type II process. Both processes occur from an electronically excited state of the ketone. Relatively few cases of Type II processes from cyclic ketones in solution have been reported[4] and this discussion is concerned primarily with the Norrish Type I reaction.

The primary product of Norrish Type I cleavage is an acyl-alkyl diradical formed by homolytic scission of the carbon-carbon bond adjacent to the carbonyl group.[5-8] With the exception of conjugated cyclopropyl ketones[9-12] and some α-cyclobutyl ketones,[13-16] the major product corresponds to cleavage of the more highly substituted

bond. However, all cases are consistent with the formation of the most stable acyl-alkyl diradical.[17-19]

The results of quenching experiments on product formation and Stern-Volmer analysis indicate that α-cleavage of non-conjugated cyclic ketones on solution photolysis occurs primarily from the triplet excited state of the ketone.[4,20-25] Decreased ring size and increased alkyl substitution enhance the rate of α-cleavage, consistent with the energy gain from the relief of strain and the increased stability of the diradical.[23]

The triplet lifetime of cyclohexanone is approximately twenty times that of cyclopentanone. Although the reasons are complex and probably involve the electronic distribution in the excited state, triplet excited states have been shown to be at least two orders of magnitude more reactive than the corresponding singlet states.[24,26] The greater importance of the triplet state in α-cleavage of ketones in solution is only partially due to the difference in the rates of reactivity of the two excited states, since experimental results cannot be accounted for solely by a rate difference. Turro discusses the difference in terms of the potential energy surfaces of the R-C=O bond.[4] In cases where the rates of intersystem crossing or radiationless decay from the singlet state are slow, partic-

ipation of that state in α-cleavage apparently becomes more significant.

The secondary reactions of the acyl-alkyl diradical determine the observed photoproducts. Figure I illustrates the pathways by which the most stable diradical for bicyclo(m.2.1)alkan-2-ones resulting from preferential α-cleavage adjacent to the bridgehead may disproportionate.

Reclosure of the radical pair results in regeneration of the starting ketone and accounts for quantum yields that are less than unity based on the observed products. If the rate of cyclization is slower than the rate of loss of stereochemistry at an asymmetric α-carbon, then racemization may occur and epimerization is observed.[27-29]

Decarbonylation is a minor reaction of cyclic ketones in solution photolysis and is generally only significant when the acyl-alkyl diradical is resonance-stabilized;[30] or in the case of strained ketones, such as cyclopropanones and cyclobutanones, in which relief of ring strain is the driving force for the reaction. Loss of carbon monoxide is sensitive to the solvent medium[31] and, since it is believed to occur from a high vibrational level of the excited singlet state, it becomes

more important at higher temperatures, particularly in the gas phase.[32,33] The resulting diradical may undergo reclosure to a cyclic hydrocarbon or intramolecular hydrogen-abstraction to a straight-chain saturated or olefinic hydrocarbon.[27,28,34,35]

The formation of ring-expanded cyclic acetals becomes significant generally when the structure of the cyclic ketone makes competing reactions unfavourable. Relief of ring strain in the case of strained systems, such as cyclobutanones, increases the importance of acetal formation.[36-42] The acetal originates from an oxycarbene intermediate, which subsequently undergoes insertion into the O-H bond of an alcoholic solvent to give the observed product.[41]

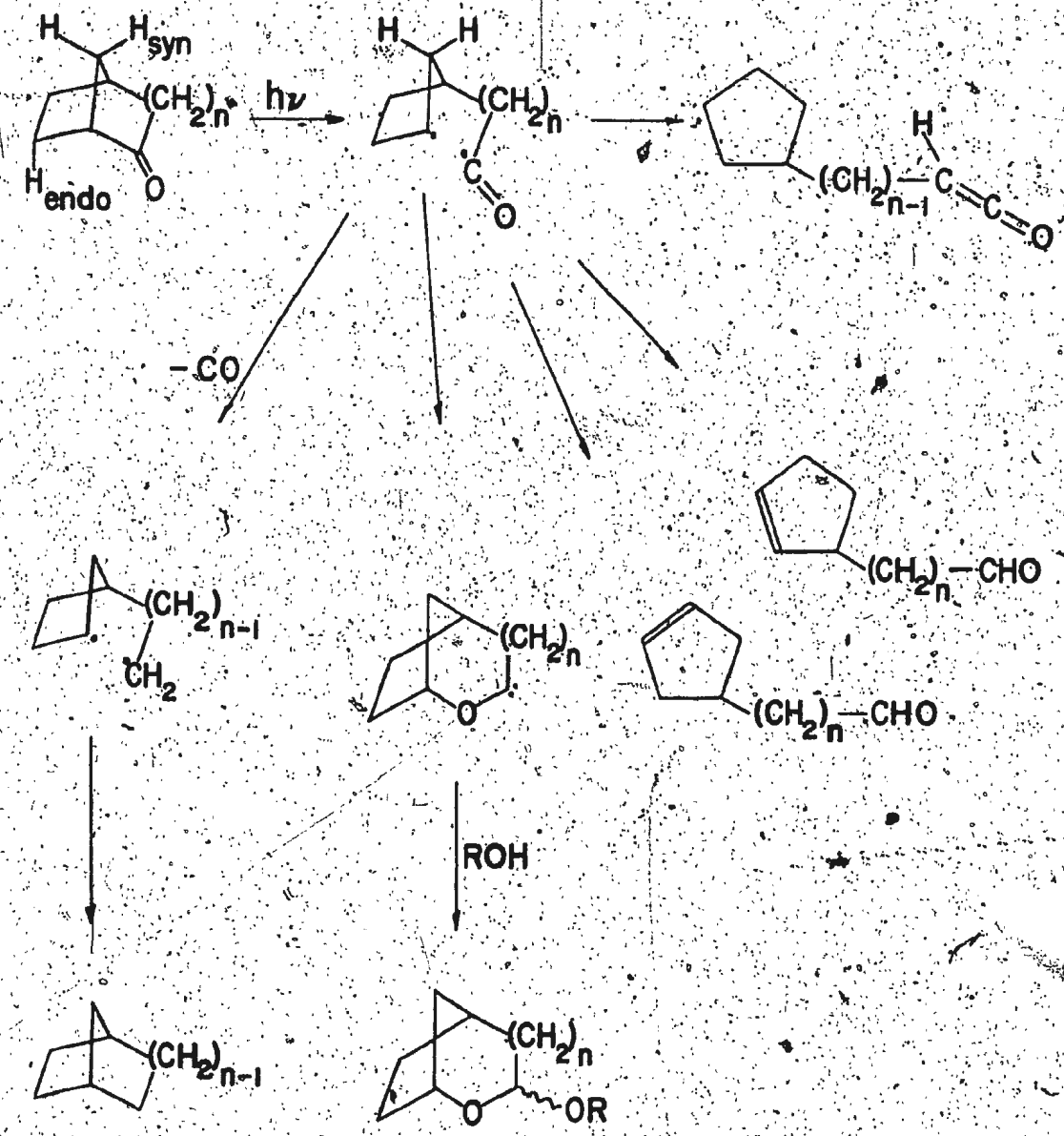
The most important photoproducts of cyclic ketones are unsaturated aldehydes and ketenes, both formed by intramolecular hydrogen-transfer to one of the radical centres from the carbon adjacent to the other. As indicated above, the bond that undergoes homolytic cleavage is that which produces the most stable diradical, dependent, in turn, on the number and nature of the substituents.[43] Subsequent stabilization by migration of a hydrogen atom, from the carbon adjacent to the acyl radical to the alkyl radical, leads to the formation of a ketene which reacts

with nucleophilic solvents to give the observed product. The ketene itself has been detected in hydrocarbon solvents by means of infrared spectroscopy with a characteristic band at approximately 2150 cm^{-1}.

Unsaturated aldehyde formation arises from intramolecular hydrogen-migration from a centre adjacent to the alkyl radical to the acyl radical. The best present evidence, based on product distributions[7,44] and chemically induced dynamic nuclear spin polarization (CIDNP) measurements,[45] is consistent with the intermediacy of discrete diradicals for this process. In addition, Coyle[46] has explained the variation of aldehyde : ketene product ratios with ring size and substitution on the basis of diradical intermediates, while deuterium labelling experiments have established the intramolecular nature of the hydrogen transfer.[17,47]

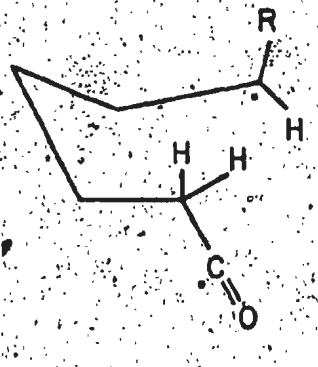
The factors governing the competition between aldehyde and ketene formation are incompletely understood. On the basis of extensive studies of simple cyclopentanones and cyclohexanones, bridged bicyclic and steroidal ketones, Quinkert concluded that, other factors being equal, the ratio of aldehyde : ketene in the irradiation of cyclic ketones is a function of the relative ring strain in the transition states leading to product.[17,48-51]

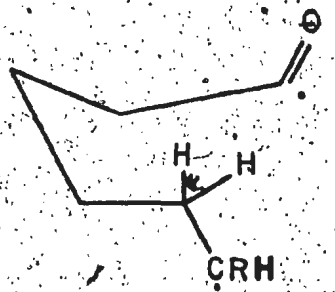
Figure I


H
H syn
(CH2)n
hν
H endo
O
H
H
(CH2)n
C
O
(CH2)n-1
H
C
C
O
-CO
(CH2)n-1
CH2
(CH2)n
O
(CH2)n
CHO
(CH2)n
CHO
ROH
(CH2)n-1
(CH2)n
O
OR

Irradiation of cyclopentanone itself by Coyle[46] in a methanol-benzene solution gave an aldehyde : ketene ratio of 20, while 2-alkyl cyclopentanones had ratios of approximately 30-40. The ratio for cyclohexanone is 1.6 and, for 2-alkyl cyclohexanones, ratios vary from 1.7 to 2.9. Clearly, ketene formation competes more favourably in the case of cyclohexanones. The results are explained by considering the conformations of the transition states leading to hydrogen transfer. A planar transition state is most favourable for the maximum overlap of orbitals in the hydrogen transfer process, but some twisting out of the plane is necessary to reduce non-bonded interactions while maintaining close proximity between the reactive centres.

In the case of cyclopentanones, the transition state for ketene formation involves more severe non-bonded interactions than that for aldehyde formation

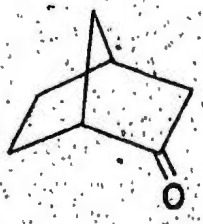




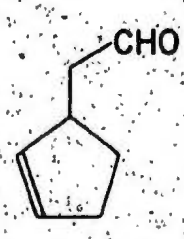
since, in the latter case, the carbonyl group is in

the ring. Therefore, aldehyde formation is favoured. The same is true for 2-substituted cyclohexanones but, in this case, the non-bonded interactions are much less serious and ketene formation is able to compete more successfully. The results of photolysis of 4-alkyl cyclohexanones provide further evidence for a cyclic transition state, since the non-bonded interactions in the transition state for aldehyde are more significant than for ketene formation.[4,46]

The photolysis of norcamphor (I) in pentane, diethyl ether and methanol led to the isolation of a single product identified as 2-cyclopentenylacetaldehyde (II).[9,24,52] This arose from abstraction of the syn-7 hydrogen rather than the endo-6 hydrogen, and therefore involves a five-membered cyclic transition state.



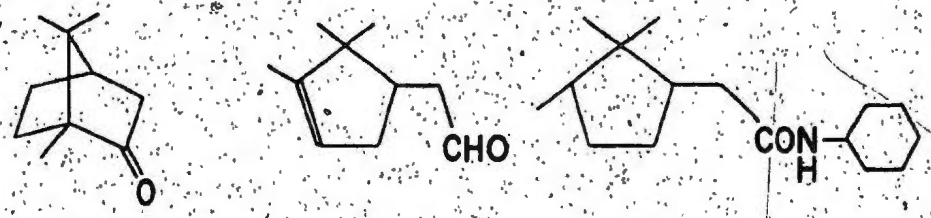
I



II

Evidence for a methyl ester, derived from a ketene intermediate, was detected when the irradiation was conducted in methanol.

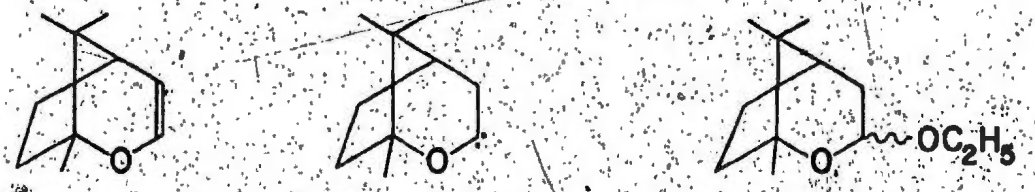
The irradiation of a related bicyclo(2.2.1) ketone, camphor (III), was first studied in 1910 by Ciamician and Silber,[53] who found that an aqueous alcoholic solution of the ketone, when exposed to sunlight for seven months, produced one major compound identified as α-campholenic aldehyde (IV). A second "ketonic" product was also claimed, but recent investigations have not substantiated this.[24,52,53] As in the case of norcamphor, no evidence was found for the formation of ketene-derived product. A minor product reported by Agosta[41] was identified as the enol ether, 1,8,8-trimethyl-2-oxabicyclo(3.2.1)oct-3-ene (VI). Deuterium labelling experiments indicate that it arises from a 1,2 hydrogen shift in the oxycarbene intermediate (VII). Photolysis in 95% ethanol provided the



III IV V

enol ether as well as the corresponding acetal (VIII), but the yield of aldehyde product remained constant.

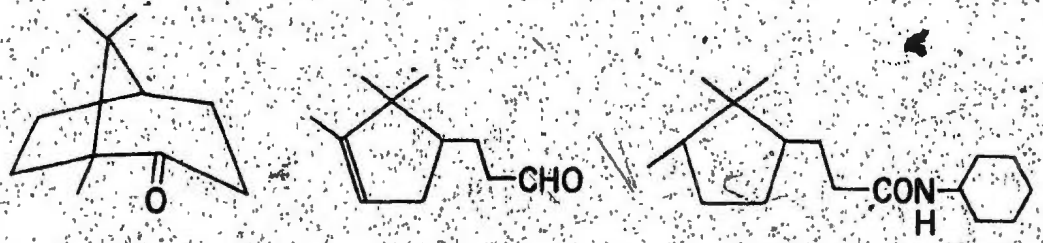
Experiments on the quenching of aldehyde formation by trans-1,3-pentadiene indicate that, in the case of both norcamphor and camphor itself, α-cleavage arises, at least partially, from the n-π* triplet state.



VI VII VIII

In contrast to norcamphor, the presence of the gem-methyl groups at the bridgehead position requires hydrogen transfer from C-6, involving a six-membered ring in the transition state, to give the unsaturated aldehyde. On the other hand, ketene formation necessitates a five-membered cyclic intermediate. Experimental evidence indicates that a six-membered ring is favoured for hydrogen abstraction leading to both aldehyde and ketene, since it involves minimal ring strain and permits the least deviation from a collinear arrangement of the centres involved. Thus, on the basis of these arguments, relatively little ketene-derived product would be expected. Quinkert detected less than 1% ketene-derived product (amide V) when an ethereal solution of camphor was

irradiated in the presence of cyclohexylamine.[17,50] In contrast, 17% of the homologous cyclohexylamide (XI) was isolated when homocamphor (IX) was irradiated.[17,50,51] There was no evidence for the formation of the unsaturated aldehyde (X).

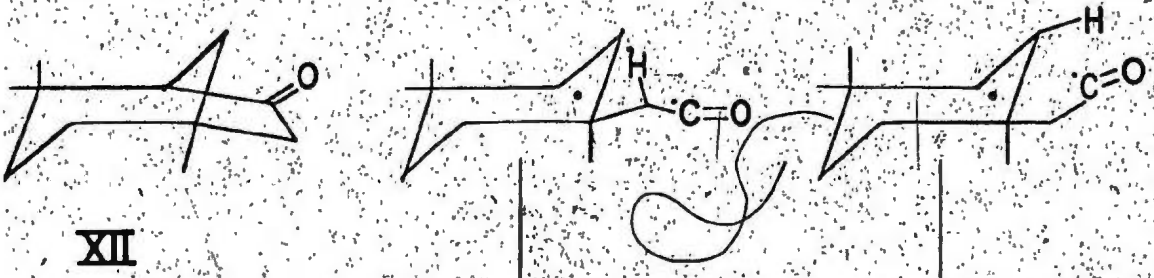


IX X XI

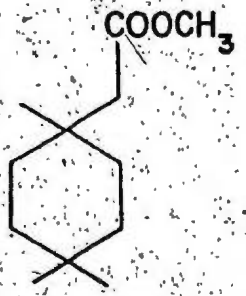
Quinkert rationalized the difference in the relative amounts of ketene-derived products in terms of the cyclic transition states involved in the hydrogen-abstraction process. In both cases, geometrical restraints require that, in the conformation for ketene formation, the substituents at the bridgehead positions are trans to each other. For camphor, the transition state leading to ketene clearly requires a strained conformation containing a five-membered ring and tends to minimize its formation when other paths are available. In contrast, the diradical produced on photolysis of homocamphor can

afford ketene via a six-membered cyclic transition state, therefore its formation is more favoured.

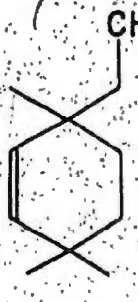
In 1972, Agosta and coworkers[55] discovered that some α,β-unsaturated cyclopentenones underwent internal cycloaddition to produce bicyclic ketones which were themselves photolabile and isomerized to unsaturated aldehyde and ketene products. Irradiation



XII



XIII



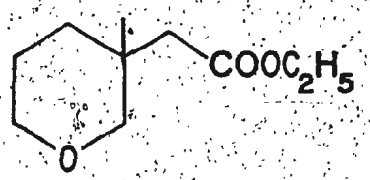
XIV

in methanol of 1,4,4-trimethylbicyclo(3.2.1)octan-6-one (XII) led to the isolation of a major product identified as 1,4,4-trimethylcyclohexaneacetic acid methyl ester

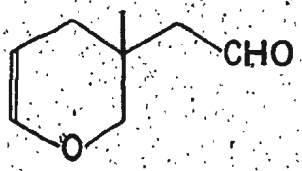
(XIII). A minor product (<10%) was tentatively assigned the unsaturated aldehyde (XIV) on the basis of its infrared spectrum and corresponds to abstraction of the syn-8 hydrogen.

Similarly, on irradiation of 1-methyl-3-oxa-bicyclo(3.2.1)octan-6-one (XV) in benzene followed by the addition of ethanol, two products were formed. A minor component (<12%) was not isolated. The major products were the ethyl ester (XVI) derived from ketene (40%), and an aldehyde (48%), presumed to be 1-methyl-3-oxacyclohexaneacetaldehyde (XVIa) from its infrared

XV



XVI

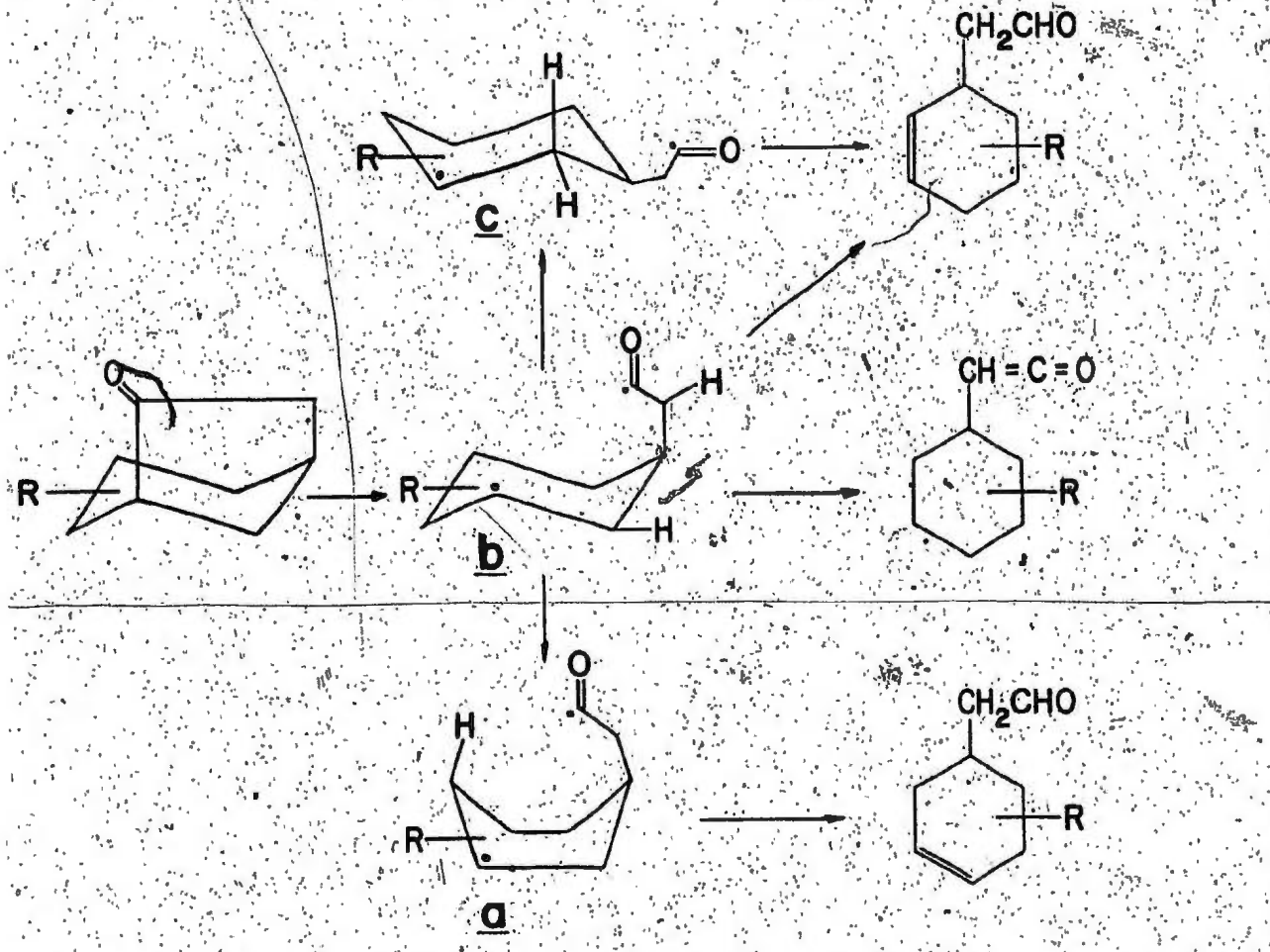


XVIa

and nuclear nagnetic resonance spectra. The difference in the aldehyde : ketene ratios for both ketones is probably a consequence of non-bonded interactions, although this is not obvious from models.

While this thesis was being written, Agosta reported results of the photochemistry of a series of

bicyclo(3.2.1)octan-6-ones.[56] Product distribution is discussed in terms of the conformation of the cyclohexyl diradical intermediates, with the assumption that the diradical has sufficient lifetime to adopt its most



stable conformation. In the case of 3-alkyl ketones, steric interaction between the acyl side chain and the

alkyl substituent are expected to force the conversion of the diradical to the alternative chair conformation c, in which both ring substituents are in equatorial positions. The predominance of aldehyde corresponding to hydrogen abstraction from this intermediate is observed with negligible ketene-derived product detected.

In the case of bridgehead substituted ketones, for example, XV discussed earlier, consideration of the steric interactions involved in the diradical intermediates anticipates more efficient competition between the chair conformation b, with axial acyl side chain, and c, with axial alkyl substituent. As expected, the aldehyde : ketene ratio approaches unity. A bulky C-1 substituent, such as the t-butyl group, is sufficient to force the diradical to assume the conformation for ketene formation, possessing the equatorial substituent to minimize non-bonded interactions, and negligible aldehyde is observed. No products which corresponded to hydrogen abstraction via the boat conformation a were detected.

As indicated by the above discussion and as Chapman has pointed out, "The factors determining the relative yields of aldehyde to ester are .... subtle (and) small changes in molecular structure .... cause

drastic alterations in the product ratios."[28] The present study was undertaken with a view to increasing our understanding of some of these factors.

DISCUSSION

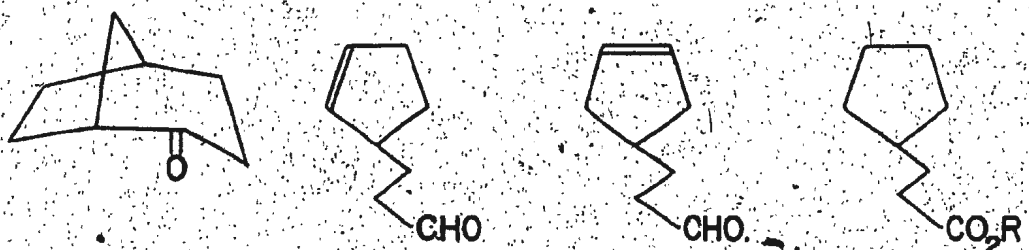
Photochemical Studies

In order to explore more fully the factors governing the behaviour of cyclic ketones in solution, a study of some bicyclic ketones was undertaken. The bicyclo(3.2.1)octan-2-ones have received little attention and the first compound chosen was XVII, for comparison with the only other previously reported example, homocamphor (IX).

Irradiation of a 0.1M. solution of the ketone in methanol in a stoppered Pyrex container, using a Hanovia 450-watt medium pressure lamp, gave a mixture, shown by g.l.c. analysis to contain three components in a ratio of 7:2:1. The n.m.r. spectrum of the mixture displayed a singlet at δ3.60 typical of methoxyl protons, complex absorption in the vinyl region, as well as a triplet at δ9.75 characteristic of an aldehydic proton. A band at 1735 cm^{-1} in the infrared spectrum suggested the carboxyl group of an ester, and peaks at 1725 cm^{-1} and at 2810 and 2705 cm^{-1} indicated the C=O and C-H stretching vibrations of an aldehyde.

Attempts to separate the major product from one

of the minor components, by thin layer chromatography in a variety of solvent systems, and by spinning-band distillation, were unsuccessful. A separation was ultimately achieved by preparative g.l.c. on a 20% Carbowax 20M column, and the fractions were obtained in a ratio of 7:2:1 for XVIII : XIX : XXb. The identification of the photolysis products is described below.



XVII XVIII XIX XX

a : R=H
b : R=CH3

The predominant product displayed infrared absorption at 2810, 2705 and 1725 cm^{-1} characteristic of an aldehyde. The n.m.r. spectrum recorded in carbon tetrachloride possessed a triplet (J=2cps) at δ9.74 consistent with an aldehydic proton adjacent to a methylene group. A multiplet representing two protons at δ5.63 was indicative of vinyl protons. On the basis of these data and further characterization of its semicarbazone, the compound was assigned the structure (XVIII).

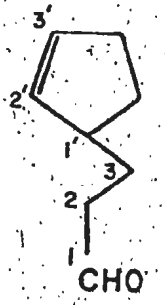
The second component obtained by preparative g.l.c. possessed similar spectral properties to the aldehyde described above, including infrared absorption at 1725 cm^{-1} and a triplet at $\delta 9.75$ in the n.m.r. spectrum. A broad triplet at $\delta 5.55$, representing two protons, indicated two equivalent protons adjacent to identical methylene groups. A structure which is consistent with these data is the aldehyde (XIX). It was further characterized as its semicarbazone derivative.

If these two photoproducts were in fact isomeric aldehydes differing only in the position of the carbon-carbon double bond, then hydrogenation of both would lead to the same product. Silver oxide oxidation of a mixture of the irradiation products, XVIII and XIX, followed by hydrogenation catalyzed by 5% palladium on charcoal provided an oil. Infrared bands at 1708, 3510, and broad absorption at 3400-3050 cm^{-1} were attributed to the C=O and O-H stretching vibrations, respectively, and broad bands at 2750-2550 cm^{-1} were typical of the O-H stretch of carboxylic acids. The absence of C=C stretch in the region of 1650-1600 cm^{-1} permitted the assignment of structure (XXa), which was confirmed by comparison with an authentic sample of 3-cyclopentylpropionic acid. The homogeneity of this acid

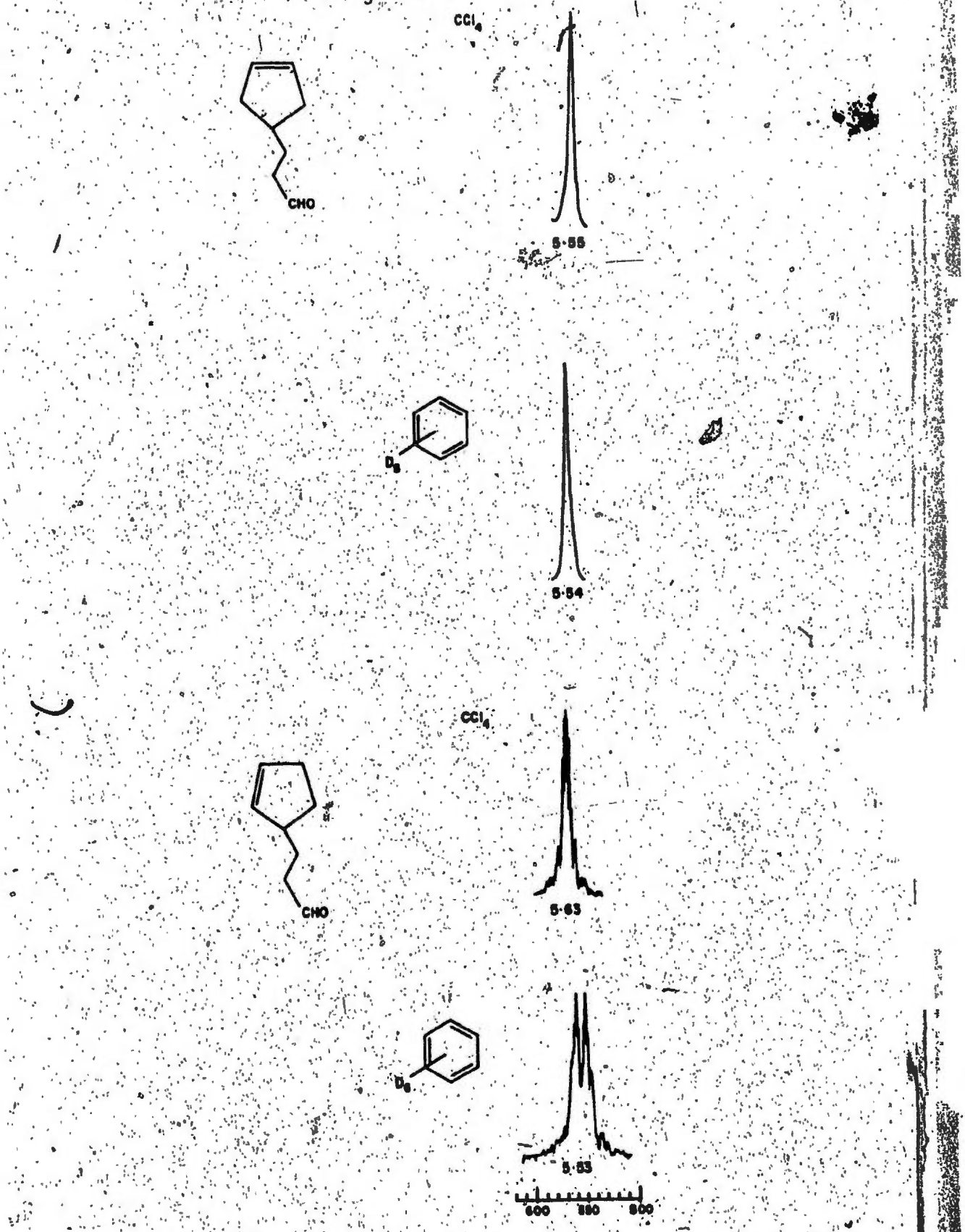
was verified by g.l.c. analysis of the sweet-smelling yellowish oil obtained after treatment with diazomethane. The infrared spectrum contained a band at 1738 cm^{-1} which was consistent with the carbonyl group of an ester. A singlet at δ3.60, representing three protons, was attributed to the methoxyl group of the expected methyl ester (XXb). A sample of methyl 3-cyclopentylpropionate was prepared from authentic acid (XXa) and compared to confirm the structure.

It was important to establish the exact position of the double bond in these isomers, to prove which hydrogen was abstracted preferentially after α-cleavage. In view of the strong directing effects of aromatic solvents on chemical shifts,[57] a shielding effect on the vinyl protons, due to bonding of the π-electron cloud of the carbonyl group with the solvent, was anticipated. The geometry of the aldehydes will cause them to experience different effects. The n.m.r. spectrum of XVIII, recorded in benzene, displayed a solvent shift of -Δδ0.1 ppm relative to carbon tetrachloride, and indicates decreased shielding of the vinyl protons. In contrast, an increased shielding effect of +Δδ0.03 ppm was experienced by the vinyl protons of the aldehyde (XIX).

More pronounced effects on chemical shifts have been observed with the use of lanthanide shift reagents.[58,59] The n.m.r. spectrum of 3-(2'-cyclopentenyl)-propionaldehyde (XVIII), in the presence of $Eu(fod)_3$ (0.8M solution of the substrate in carbon tetrachloride; 0.5M in $Eu(fod)_3$), was recorded, and the peaks assigned by analogy with a similar spectrum of methyl 3-(2'-cyclopentenyl)propionate.[60] A triplet (J=7 cps) at δ9.74 was attributed to the C-2 methylene protons, in accord with the effect expected due to the close proximity to the carbonyl group coordinated with the europium



complex. Multiplets at δ6.7 and 5.5, representing one proton each, were assigned to the C-2' and C-3' vinyl protons, respectively, and correspond to a chemical shift of approximately 1 ppm relative to the spectrum in the absence of shift reagent. A quartet at δ6.43 (J=6 cps) and a broad signal at δ5.1 were attributed to the C-3 methylene and the C-1' methine protons, respectively. Assignment of the more complex absorption at higher field was not possible. Presumably, if the side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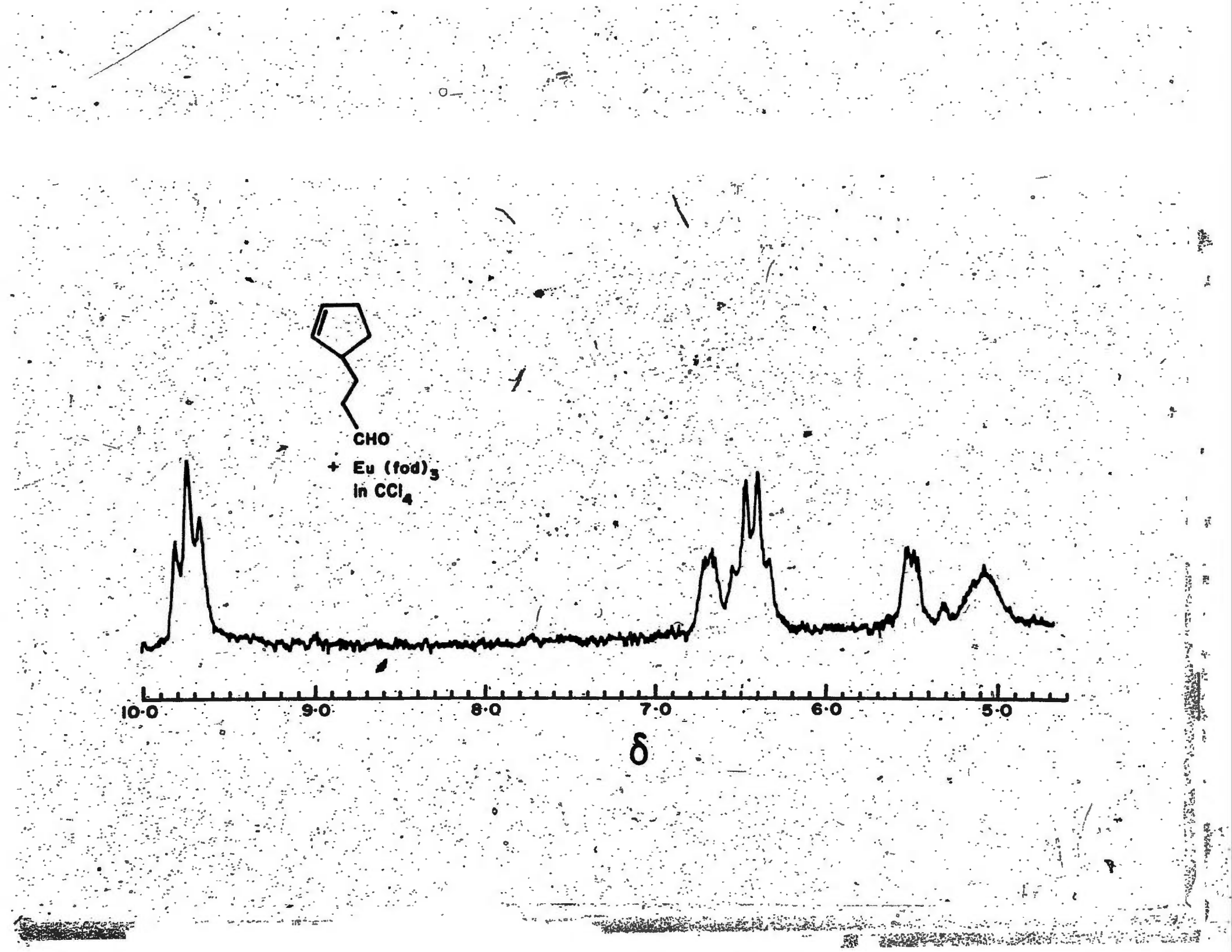
CHO
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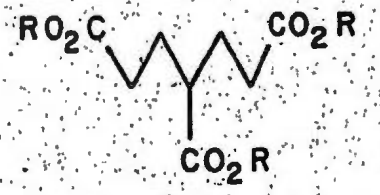
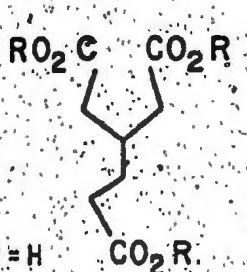
chain sits under the molecule, the endo ring hydrogens experience a larger solvent-induced shift than the exo hydrogens.

The aldehydes (XVIII and XIX) were further characterized by degradation. Oxidative cleavage of the carbon-carbon double bond was achieved by ozonolysis of the carboxylic acids obtained by silver oxide oxidation of a mixture of the aldehydes. Oxidative decomposition of the resulting ozonides, and subsequent *in situ* methylation by the addition of diazomethane, provided a neutral oil with a sweet odour. G.l.c. analysis indicated two components as expected.

The n.m.r. spectrum displayed singlets at δ3.63 and 3.65 in a ratio of 2:1 typical of methoxyl protons, and suggested that the major product was the symmetrical ester (XXIb). Additional methoxyl absorption for the minor component at δ3.43 and 3.83 (2:1) permitted the



a: R = H
b: R = CH_3 XXI



a: R = H
b: R = CH_3 XXII

assignment of structure (XXIIb). Integration of the respective signals indicated the two triesters were present in a ratio of 6:1 (XXIb : XXIIb).

Attempts to isolate the degradation products as

the tricarboxylic acids (XXIa and XXIIa) by extraction of the aqueous methanolic ozonolysis mixture were unsuccessful in view of the highly polar nature of the acids, which were soluble in the aqueous medium. The addition of sodium chloride to make a saturated solution failed to force the product into the organic phase.

A sample of dimethyl 3-carbomethoxy-1,7-heptanedioate (XXIb) was prepared by the addition of diazomethane to authentic 3-carboxy-1,7-heptanedioic acid obtained from Aldrich (pentane-1,3,5-tricarboxylic acid), and the n.m.r. spectrum compared with the ozonolysis product. Peaks at δ3.65 and 3.63, representing three and six protons, respectively, were attributed to the methoxyl protons and were in agreement with the peaks assigned to the major product of the degradation mixture.

The identification of the minor ester (XXIIb) was now possible on the basis of the n.m.r. and infrared spectral properties of the total product and on the unequivocal establishment of the structure of the ester (XXIb).

The third photolysis product was isolated from the crude irradiation mixture as a neutral oil by ethereal extraction of the basic silver oxide-aldehyde solution. Methoxyl absorption at δ3.6 in the n.m.r. spectrum and an infrared band at 1735 cm^{-1} suggested a methyl ester.

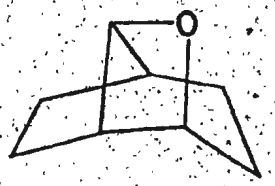
G.l.c. analysis of this compound, the methyl ester obtained from the isomeric aldehydes as described above, and an authentic sample of methyl 3-cyclopentylpropionate, revealed that all three compounds possessed the same retention time. Their n.m.r. and infrared spectra were identical, permitting the structure (XXb) to be assigned to the third irradiation product.

Irradiation of bicyclo(3.2.1)octan-2-one as before in a 1:1 mixture of tetrahydrofuran : water provided the isomeric aldehydes (XVIII and XIX) in a ratio of 8:2, identified by comparison with the methanolic photoproducts. Examination of the relative intensities of the triplet at δ9.75 and the broadened singlet at δ10.1 in the n.m.r. spectrum, assigned to the aldehydic and carboxylic acid protons, respectively, in conjunction with g.l.c. analysis of the aldehydes, permitted the calculation of a product distribution ratio of 8:2:1 for XVIII : XIX : XXa.

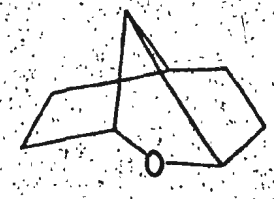
Extraction of the total photolysis mixture with aqueous sodium bicarbonate , acidification of the aqueous phase and extraction with ether provided the third component, expected to be structure (XXa) on the basis of the methanolic irradiation. Infrared bands at 1708 cm^{-1}, due to carbonyl absorption, O-H stretching bands at 3510 and 3400-3050 cm^{-1}, as well as the broad absorption at 2750-2550 cm^{-1} typical of carboxylic acids, were

identical with an authentic sample of 3-cyclopentyl-propionic acid. A broadened singlet at δ10.13 in the n.m.r. spectrum, attributed to the carboxylic acid proton, was consistent with the assigned structure.

After prolonged photolysis of XVIII, g.l.c. analysis (Column A) revealed that the aldehyde peak diminished in intensity, coincident with the appearance of a peak at shorter retention time. The n.m.r. spectrum of a sample of the unknown, obtained by preparative g.l.c., displayed complex absorption at δ2.9 and 3.8 and lacked the presence of aldehydic proton absorption. In addition, the infrared spectrum possessed no bands in the carbonyl region. This evidence suggests an internal



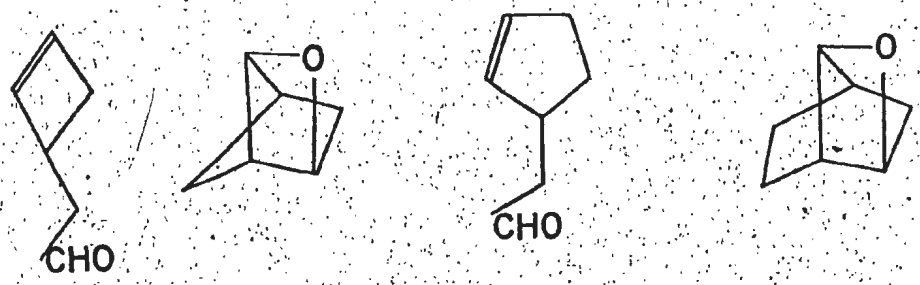
A



B

Paterno-Buchi reaction to form an oxetane. Intramolecular cycloaddition of the carbonyl group of the aldehyde (XVIII) to the double bond can proceed in two directions to give oxetanes A or B. Analogous oxetane formation was discovered by Meinwald and Chapman[52,61] on prolonged irradiation of the aldehydes, XXIII and XXIV, photo-

products from bicyclo(2.1.1)hexan-2-one and bicyclo(2.2.1)-heptan-2-one, and the structures were established by pyrolytic degradation and lithium aluminum hydride reduction as XXIIIa and XXIVa, respectively. On the basis of

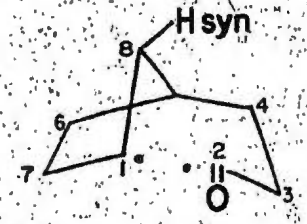


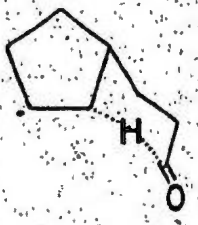
XXIII XXIIIa XXIV XXIVa

these observations and related examples,[62-67] the less strained oxetane A is proposed. Insufficient material was obtained to enable proof of the structure by degradation, and it was not possible to choose between the two structures by means of the n.m.r. spectrum.

As mentioned earlier, recent evidence supports the formation of discrete diradicals as primary photoproducts in the α-cleavage of cyclic ketones. The presence of a diradical intermediate from bicyclo(3.2.1)octan-2-one has recently been observed by means of chemically induced dynamic nuclear spin polarization (CIDNP).[45] The photolysis products arise from cleavage of the bond between the carbonyl group and the bridgehead carbon, as expected on the basis of relative radical stabilities.[19]

The preferential formation of aldehyde (XVIII), may be rationalized in terms of the conformation of the transition state for the product. Disproportionation to XVIII by abstraction of the syn-8 hydrogen by the acyl radical involves a six-membered cyclic transition state. Examination of molecular models (Prentice-Hall, Dreiding) revealed that, after flipping of the cyclopentane ring, the acyl carbon is able to get close enough to the syn-8 hydrogen that abstraction may readily occur. The resulting fused ring system approaches a cis-hydrindane as indicated. If the six-membered ring

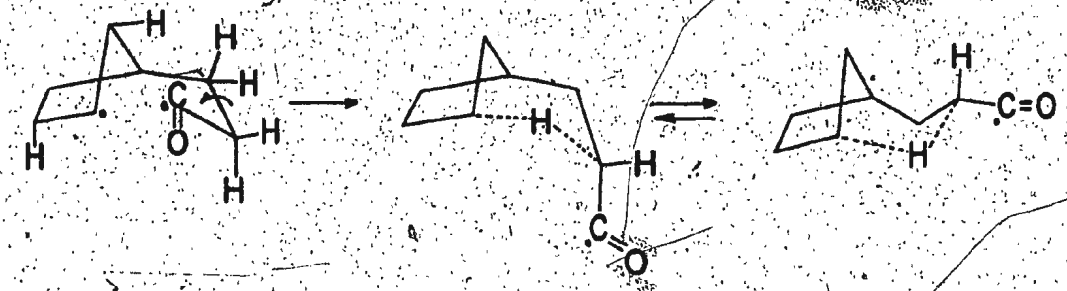




retains a boat conformation, models indicate non-bonded interactions between the endo-6 and endo-3 hydrogens. In contrast, the chair conformation permits close proximity of the reactive centres while reducing these non-bonded interactions, thereby favouring the formation of aldehyde (XVIII).

The formation of 3-cyclopentylpropionic acid (XXa) and the methyl ester (XXb) in aqueous and methanolic

media, respectively, corresponds to the reaction of ketene with the nucleophilic solvent. Ketene formation involves abstraction of a hydrogen adjacent to the carbonyl group, and also occurs through a six-membered cyclic transition state. By examination of a model of the diradical intermediate, it is evident that rotation about the C_3-C_4 bond is necessary to bring the reactive centres close enough for reaction to occur. The most

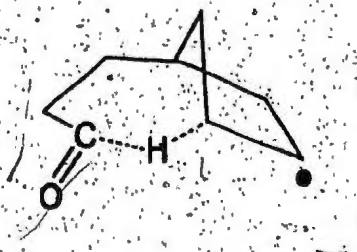


likely path involves anti-clockwise rotation in order that severe steric interaction between the bridge methylene group and the acyl radical is avoided. Rotation in this sense allows the abstraction of the <u>exo</u>-3 hydrogen. Clearly, if the six-membered ring exists in the chair conformation, non-bonded interactions will occur between the axial acyl side chain and the <u>endo</u>-7 hydrogen. These are reduced if the higher energy twist boat form, in which the side chain is in an equatorial position, is adopted. Eclipsing of the axial C-3 and the bridge <u>syn</u> hydrogen atoms, that results when the

transition state adopts the boat conformation, is probably less severe than the hydrogen-acyl interaction in the chair form, although the twist boat form itself is less stable.[68,69]

Of greater importance, these conformations required for ketene formation are of a bridged ring type, and lie intermediate to a bicyclo(2.2.1) and a bicyclo(3.2.1) system, involving more 'strain' than the corresponding hydrindanone intermediate (see Table I), such that the aldehyde (XVIII) is formed in preference.

The minor photolysis product, aldehyde (XIX), results from endo-7 hydrogen abstraction by the acyl radical via a seven-membered cyclic transition state. The greater torsional strain involved in a seven-membered ring com-



pared to a six-membered ring is evident from both the relative heats of combustion and the strain energies.

The transition state for XIX approaches a bicyclo-(4.2.1)nonanone system, and considerably more strain is

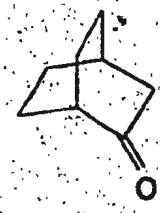
Table I

Calculated Strain Energies[72]	(kcal. mol^{-1})
Cyclohexane	1.43
Cyclopentane	7.28
Cycloheptane	7.65
trans-Bicyclo(4.3.0)nonane (trans-hydrindane)	8.76
Bicyclo(3.3.1)nonane	9.59
cis-Bicyclo(4.3.0)nonane (cis-hydrindane)	9.86
Bicyclo(3.2.1)octane	12.06
Bicyclo(2.2.2)octane	12.95
Bicyclo(2.2.1)heptane	16.98
Bicyclo(4.2.1)nonane	20.95

required to place the acyl radical in close enough proximity for abstraction to take place. The boat conformation for the transition state causes steric interaction between the C-6 axial and the C-3 axial hydrogen atoms. The preferred conformation is the chair form, in which non-bonded interactions are reduced. Thus, the low yield of aldehyde (XIX) is accounted for in terms of the increased strain in the transition state relative to XVIII.

In order to more completely understand the factors influencing product distribution, a system was selected in which both the ketene and the aldehyde arise from different bridged ring systems, each of which will involve a six-membered ring in the transition state.

Irradiation of a 0.1M methanolic solution of XXV in Pyrex for four hours gave a mixture whose infrared spectrum displayed carbonyl absorption at 1725 and 1738 cm^{-1}. The main features of the n.m.r. spectrum of the mixture were a triplet at δ9.68 (J=1.5 cps), a broad signal at δ5.60, and sharp singlet at δ3.62. Calculation of the relative



XXV

XXVI

XXVII

a: R = H
b: R = CH_3

XXVIII

a: R = H
b: R = CH_3

intensities from the aldehyde peak at δ9.68 and the methyl ester signal at δ3.62 indicated a ratio of 4:1 for aldehyde : ester.

Silver oxide oxidation of the aldehyde to the corresponding carboxylic acid enabled the separation of this material from the mixture and permitted the isolation of the second component. Ethereal extraction of the basic silver

oxide solution provided an oil. Infrared absorption at 1735 cm^{-1} and a signal at δ3.62 in the n.m.r. spectrum suggested a methyl ester, and the compound was tentatively assigned the structure (XXVIIb). Methyl 3-cyclohexenylacetate was prepared by an independent synthesis from 3-cyclohexenylcarboxylic acid via the acid chloride and the diazoketone, and the resulting 3-cyclohexenylacetic acid treated with diazomethane to provide the methyl ester. Infrared and n.m.r. spectral comparison of the hydrogenated material with the irradiation product confirmed the structure of the latter.

Acidification of the basic silver oxide solution and ethereal extraction provided a colourless oil. The n.m.r. spectrum displayed peaks at δ11.77, typical of a carboxylic acid, and a singlet at δ5.57, representing two protons, indicative of olefinic protons. Infrared bands at 3500-3100, 2750-2550, and at 1710 cm^{-1} were consistent with a non-conjugated carboxylic acid, and proof that the compound had the structure (XXVIIIa) was shown by comparison of the infrared and n.m.r. spectral properties of 3-cyclohexenylacetic acid, prepared independently as described above.

The photolysis of bicyclo(2.2.2)octan-2-one in a 1:1 mixture of tetrahydrofuran : water was conducted for seven hours. The n.m.r. spectrum of the mixture with a

triplet at δ9.63 and a broadened singlet at δ11.35 indicated the photolysis products were present in a ratio of 10:1 (XXVI : XXVIIa). An oil was isolated after extraction of the mixture with sodium bicarbonate. Infrared absorption at 2810, 2700, and at 1725 cm^{-1} and a triplet at δ9.63 in the n.m.r. spectrum were consistent with an aldehyde. In addition, unsaturation was indicated by a peak at δ5.57. Comparison of the n.m.r. and infrared spectra with those of the aldehyde obtained on methanolic photolysis revealed they possessed the same structure (XXVI).

After acidification of the basic extract from the photolysis mixture and extraction with diethyl ether, a colourless oil was obtained. The structure (XXVIIa) was assigned to this compound by spectral comparison with authentic cyclohexylacetic acid.

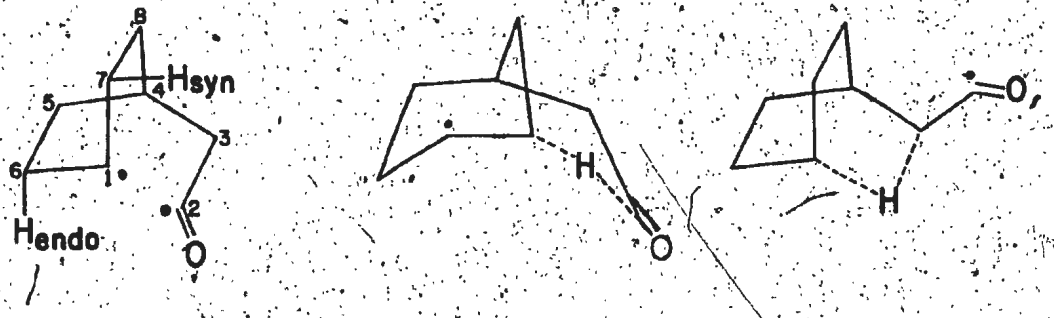
The predominant product of the irradiation of XXV is the unsaturated aldehyde (XXVI), and results from abstraction by the acyl radical of the geometrically equivalent endo-6 or the syn-7 hydrogen adjacent to the alkyl radical.

---

*In a recent communication concerning the deuterium isotope effects on the photolysis of endo-5,6-dideuteriobicyclo(2.2.2)octan-2-one, the only product isolated was the d_2-aldehyde. No ketene product was detected when the irradiation was conducted in benzene with added methanol.[70]

The rigidity of the ketone requires that the cyclohexane ring exist in the less stable boat conformation with eclipsing of the C-5 and C-6, as well as the C-7 and C-8, methylene groups. After α-cleavage, the six-membered ring is free to flip into its more stable chair conformation, relieving the eclipsing. In addition, the syn-7 moves into closer proximity to the acyl radical for abstraction to occur.

In contrast, the transition state for ketene formation approaches the geometry of a bicyclo(2.2.2)octane, inducing strain (see Table I) and causing eclipsing of methylene groups. Such a transition state is less stable



relative to the ketone itself, since cyclohexanone boats are relatively more stable than the corresponding boat and chair forms of cyclohexanes.[71] In addition, the boat conformation forces the acyl side chain into an axial position with respect to one of the two-carbon bridges, thereby increasing non-bonded interactions.

It is evident from a comparison of the calculated

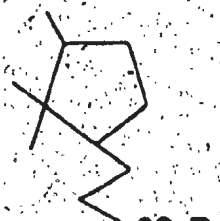
strain energies (Table I), that the transition state for ketene is intermediate to a bicyclo(2.2.1) and a bicyclo-(2.2.2) system, and is therefore less favoured than that which approaches the bicyclo(3.3.1) system required for the formation of aldehyde.

Clearly, a consideration of strain energies alone is insufficient to explain the photolytic behaviour of cyclic ketones, as evidenced by the formation of the aldehyde (XIX) on irradiation of XVII. If differences in strain energies alone determined the fate of the diradical intermediate, then a comparison of the higher energy of the bicyclo(4.2.1)-nonane type intermediate, relative to the other available pathways, should render the formation of XIX prohibitive. In view of the behaviour of XVII on irradiation, it was felt that a further investigation was warranted of the related bicyclo(3.2.1)octan-2-one, homocamphor (IX), previously examined by Quinkert, who found no evidence of aldehyde formation.[17,50] It should provide a direct measure of the competition between the bicyclononane and bicyclooctane intermediates leading to aldehyde and ketene, respectively.

A 0.1M solution of homocamphor in methanol was irradiated in Pyrex for seven hours to provide a colourless oil, shown by g.l.c. analysis to be a mixture of two components. The n.m.r. spectrum of the mixture displayed a triplet at

δ9.67 (J=1.5 cps) and a multiplet at δ5.15, suggesting the presence of aldehydic and vinyl protons. A singlet at δ3.60 indicated the methoxyl protons of a methyl ester. Examination of the relative intensities of the peaks at δ9.67 and 3.60 permitted the calculation of a ratio of approximately 4:1 for aldehyde : ester.

Separation of the two components was achieved by removal of the aldehyde following oxidation to its corresponding carboxylic acid. Ethereal extraction of the basic solution obtained on treatment of the irradiation mixture with silver oxide provided the minor component. An infrared band at 1740 cm^{-1} and methoxyl absorption at δ3.60 were consistent with a methyl ester, and the compound was tentatively assigned the structure (XXIXb).



XXIX

XXX

a: R=H
b: R=CH_3

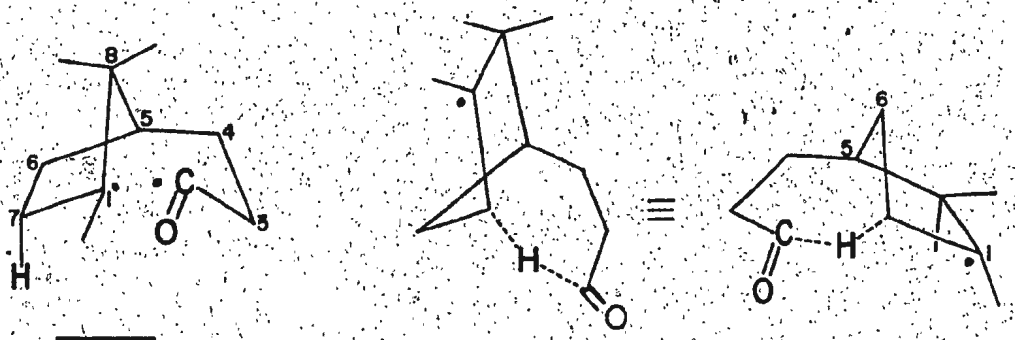
After acidification of the basic silver oxide solution and extraction with diethyl ether, an oil was obtained, which possessed infrared absorption at 1705 and 3500-3100 cm^{-1} and peaks at δ5.15 and 12.0 in the n.m.r. spectrum. Compar-

son with the spectra of the known compound permitted the assignment of the unsaturated carboxylic acid (XXX),[73] and established the major photolysis product as the aldehyde (X).

Homocamphor was irradiated as before in a 1:1 mixture of tetrahydrofuran : water for four hours and extracted with aqueous sodium bicarbonate to provide a neutral oil, identified as the unsaturated aldehyde (X) by comparison with the methanolic photoproduct. Acidification of the basic phase and extraction with diethyl ether afforded the second component as an oil, which displayed infrared absorption at 3500-3100 and 2700-2400 cm^{-1}, and at 1705 cm^{-1}, typical of the O-H and C=O stretching bands of a carboxylic acid, as well as a broad singlet at δ12.0 in the n.m.r. spectrum. The structure (XXIXa) was assigned by agreement of the spectral properties with those of the known compound.[73] Calculation of the relative intensities of the peaks at δ9.64 and 12.0 in the n.m.r. spectrum of the mixture provided a product distribution ratio of 30:1 for X : XXIXa. Confirmation of the structure of the methyl ester (XXIXb) from the methanolic irradiation was now possible by the unequivocal identification of the carboxylic acid (XXIXa).

The preferential formation of the aldehyde (X) on irradiation of homocamphor in both methanol and tetrahydrofuran was initially surprising in view of the fact that

Quinkert detected only ketene when the photolysis was conducted in diethyl ether. As indicated above, the formation of the aldehyde (XIX) from the unsubstituted analogue (XVII) suggested that the aldehyde (X) should be a minor product, since the transition states for both involve the same bicyclic ring system. A comparison of the conformations of the transition states for ketene and aldehyde formation is required to explain the product distribution.

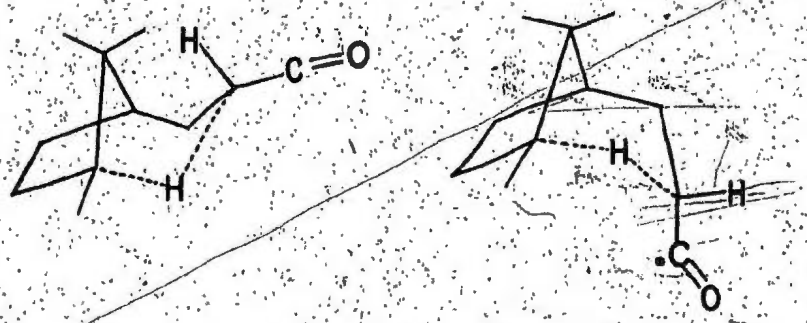


XXXI

The transition state for aldehyde approaches a bicyclo(4.2.1)nonanone system, in which the endo-7 hydrogen is abstracted by the acyl radical. Consideration of the relative strain energies for bicyclo(4.2.1)nonane, bicyclo(3.2.1)octane and bicyclo(2.2.1)heptane suggests that the formation of aldehyde is prohibited by the higher energy of its transition state. However, the introduction of a carbonyl group into the twist-chair conformation for cycloheptane has been shown to lower the calculated steric energy by 1.5 Kcal.[71] Therefore, the value in Table I for

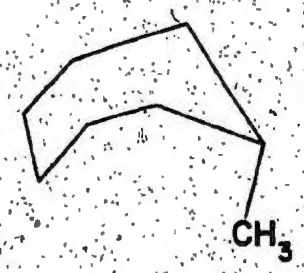
bicyclo(4.2.1)nonane is probably lowered for the bicyclic transition state for aldehyde.

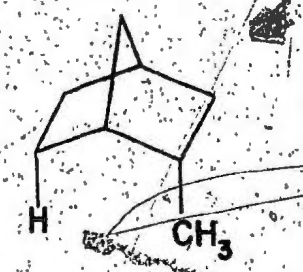
Abstraction of a C-3 hydrogen by the alkyl radical leads to ketene and proceeds via a six-membered cyclic transition state. As in the case of XVII, rotation of the C_3-C_4 bond of XXXI in an anticlockwise direction minimizes steric interaction between the acyl side chain and the syn-8 methyl group. The transition state lies intermediate to a bicyclo(2.2.1) and a bicyclo(3.2.1) system.



The energy difference of approximately 7 Kcal per mole between the chair and the higher energy boat forms of bicyclo(3.2.1)octane[74,75] is expected to be increased by steric interaction of the syn-8 methyl with the C-3 axial substituent. The chair conformation involves the less serious interactions between the axial side chain and the endo-6 and endo-7 hydrogens, as well as allowing the six-membered ring to exist in its more stable chair form.[68]

The degree of interaction can be estimated by comparing the seven-membered ring in the transition state to a methylcycloheptane. An axial methyl in the boat conformation of cycloheptane causes an increase in energy of 5.3 Kcal per mole in excess of the strain energy.[69] In view of the bicyclic nature of the transition state and the axial acyl substituent, this interaction is probably more severe than in the simple cycloheptane. In contrast, the increase in the total strain energy of endo-2-methylnorbornane (XXXII) is approximately 1 Kcal relative to norbornane itself.[72]





XXXII

The hydrogen-abstraction process can also be considered to approach a system containing a cis-1,3-diaxialdimethyl interaction. The magnitude of this interaction has been calculated for cis-1,3-diaxialdimethylcyclohexane to be 3.7 Kcal,[76] and a value of 5.9 Kcal, including gauche

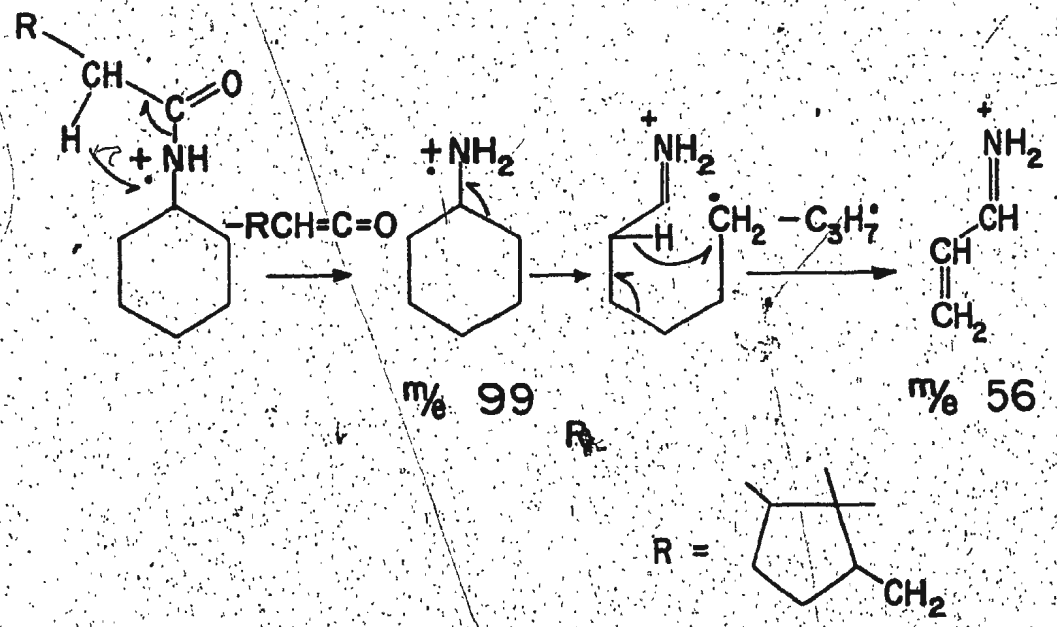
interactions, has been found experimentially.[77] Interactions involving the acyl substituent with the C-6 and C-7 methylenes are expected to be at least as serious as methyl-methyl interactions. These interactions will be present in both bicyclo(3.2.1)octan-2-one and homocamphor so that aldehyde should predominate, as has been found. However, the methyl groups in homocamphor may cause the five-membered ring to be more splayed and result in enhanced transition state interaction.

Thus, the predominance of aldehyde over ketene formation must be explained in terms of the relative strain energies and steric interactions in the transition states. In view of the formation of the aldehyde on photolysis in both methanol and tetrahydrofuran : water, a reexamination of the reaction in diethyl ether, under conditions identical to Quinkert's, was considered warranted.

A 0.25M solution of homocamphor in diethyl ether, containing cyclohexylamine, was irradiated for forty-eight hours. Careful monitoring by g.l.c. indicated that no aldehyde was formed during the reaction. A precipitate that was produced was presumed to be the cyclohexylamide (XI) discovered by Quinkert. The large discrepancy in the melting point of 206.5-207.5°C of the material obtained after recrystallization from chloroform-benzene and the value of 50-55°C reported by Quinkert,[51] is per-

haps accounted for by the possible impurity of Quinkert's product (melting range of 5°) and by his use of optically active ketone. Whereas racemic material generally melts at a lower temperature than the (+)- or the (-)-compound, several cases of the reverse have been known.[78]

The n.m.r. spectrum displayed a broad signal at δ7.9, indicative of amide absorption. However, a band at 1705 cm^{-1} in the infrared spectrum did not coincide with Quinkert's value of 1640 cm^{-1} for the carbonyl stretching frequency of the cyclohexylamide. A positive ninhydrin test implied an amine or an amide, and the former was precluded by washing of the precipitate with dilute acid. The pure material was soluble only in very polar solvents and was undetectable by g.l.c. analysis. While it is perhaps surprising that the mass spectrum displayed no peaks corresponding to ions great-



er than mass 100, the base peak at m/e 56 and the second most abundant peak at m/e 99 can be accounted for by a fragmentation process involving cleavage of the N-C=O bond, as shown.[79]

Thus, in spite of the apparent contradictory experimental evidence, the product is likely the expected amide (XI), but preparation of more homocamphor and reinvestigation of the photolysis is required for unequivocal proof of structure.*

In contrast, when a solution of homocamphor in diethyl ether, containing tetrahydrofuran in addition to cyclohexylamine, was irradiated for ten hours, the oil obtained after workup was shown by g.l.c. analysis to contain the aldehyde (X). The infrared spectrum of the mixture contained carbonyl bands at 1725, 1710 and 1670 cm^{-1}, suggesting the presence of aldehyde, ketone and the expected amide.

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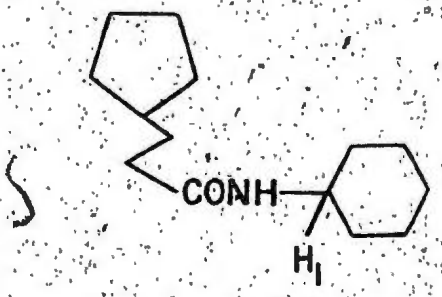
* In line with a referee's suggestion, the sample may contain some cyclohexylamine hydrochloride due to its partial solubility in water. However, a possibility that the compound is a nitrile is supported by a positive reaction on pyrolysis in molten sulphur[80] and by the strong band at 2250 cm^{-1} in the infrared spectrum. Continuing work is being carried out to determine the exact nature of the photolysis product.

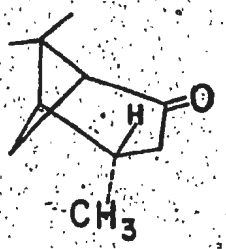
In view of the results of the ethereal photolysis of homocamphor, it was felt of interest to investigate the unsubstituted bicyclo(3.2.1)octan-2-one (XVII) under the same reaction conditions to determine whether aldehyde formation was suppressed in a similar manner. G.l.c. analysis of the yellow oil isolated after a 0.25M solution of the ketone in diethyl ether containing cyclohexylamine was irradiated for forty hours indicated that the reaction was approximately 30% complete. After extraction of the mixture with dilute hydrochloric acid, the n.m.r. spectrum displayed broad signals at δ4.20 and 9.68, attributed to the H_1 and aldehyde protons, respectively. Calculation of the relative intensities provided a ratio of 1:2.5 for aldehydes : amide. A band at 1665 cm^{-1} represented the carbonyl group of the cyclohexylamide (XXXIII).*



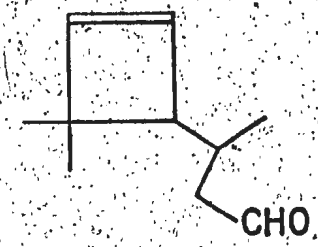
XXXIII

* Prolonged photolysis of the amide (XXXIII) resulted in the formation of a compound whose infrared spectrum displayed a band at 2250 cm^{-1} and lends support to a nitrile structure for the unknown substance obtained when homocamphor was irradiated in cyclohexylamine.

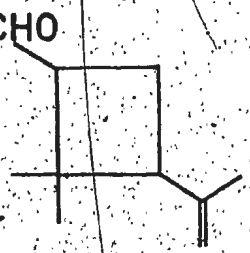
The effect of diethyl ether on product distribution is surprising in view of the results of photolysis in tetrahydrofuran. An example of the effect of solvent on the course of a related photochemical reaction was recently demonstrated by the ketone (XXXIV). Irradiation in methanol produced the aldehydes (XXXV and XXXVa) in a 1:2



XXXIV



XXXV



XXXVa

ratio, while in tetrahydrofuran, XXXV was formed almost exclusively.[81] Possibly, preferential solvation of the diradical occurs, altering the quantum yield, resulting in preferential ring closure.

The amine is probably the key feature, modifying the nature of the interactions by associating with the ketone, and hence the acyl radical, resulting in increased heptane interactions. It may solvate the diradical preferentially in comparison with water or methanol, facilitating ketene formation at the expense of hydrogen abstraction to give aldehyde. Further investigation is

thus warranted, with the possible use of water or a less bulky amine in an ethereal solution of the ketone. The ability to tip the balance by judicious choice of solvent is of considerable potential synthetic utility.

Table II

Ketone	Solvent	Ald *syn*-8	Ald *endo*-7	Ketene
Bicyclo(3.2.1)-octan-2-one	MeOH	7	2	1
	$THF-H_2O$	8	2	1
	$Ether-RNH_2$	1		2.5
Bicyclo(2.2.2)-octan-2-one	MeOH		4	1
	$THF-H_2O$		10	1
Homocamphor	MeOH		4	1
	$THF-H_2O$		30	1
	$Et_2O-THF-RNH_2$		1	1
	Et_2O-RNH_2		0	1

Mass Spectra

The mass spectra of the bicyclic ketones (XVII, XXV, IX) and their α-deuterated analogues were studied. Fragmentation pathways are presented to account for the major mass spectral peaks observed. Few cases of related bicyclic systems have been reported,[82-91] making generalizations difficult.

The α-deuterated bicyclic ketones were prepared for comparison of their mass spectral fragmentation patterns with those of the non-deuterated analogues. A dioxane solution of the ketone was treated with a solution of sodium hydroxide in deuterium oxide and the reaction stirred at 45° for six days.[92] Extraction with diethyl ether provided the deuterated ketones in yields ranging from 75% to 99%.

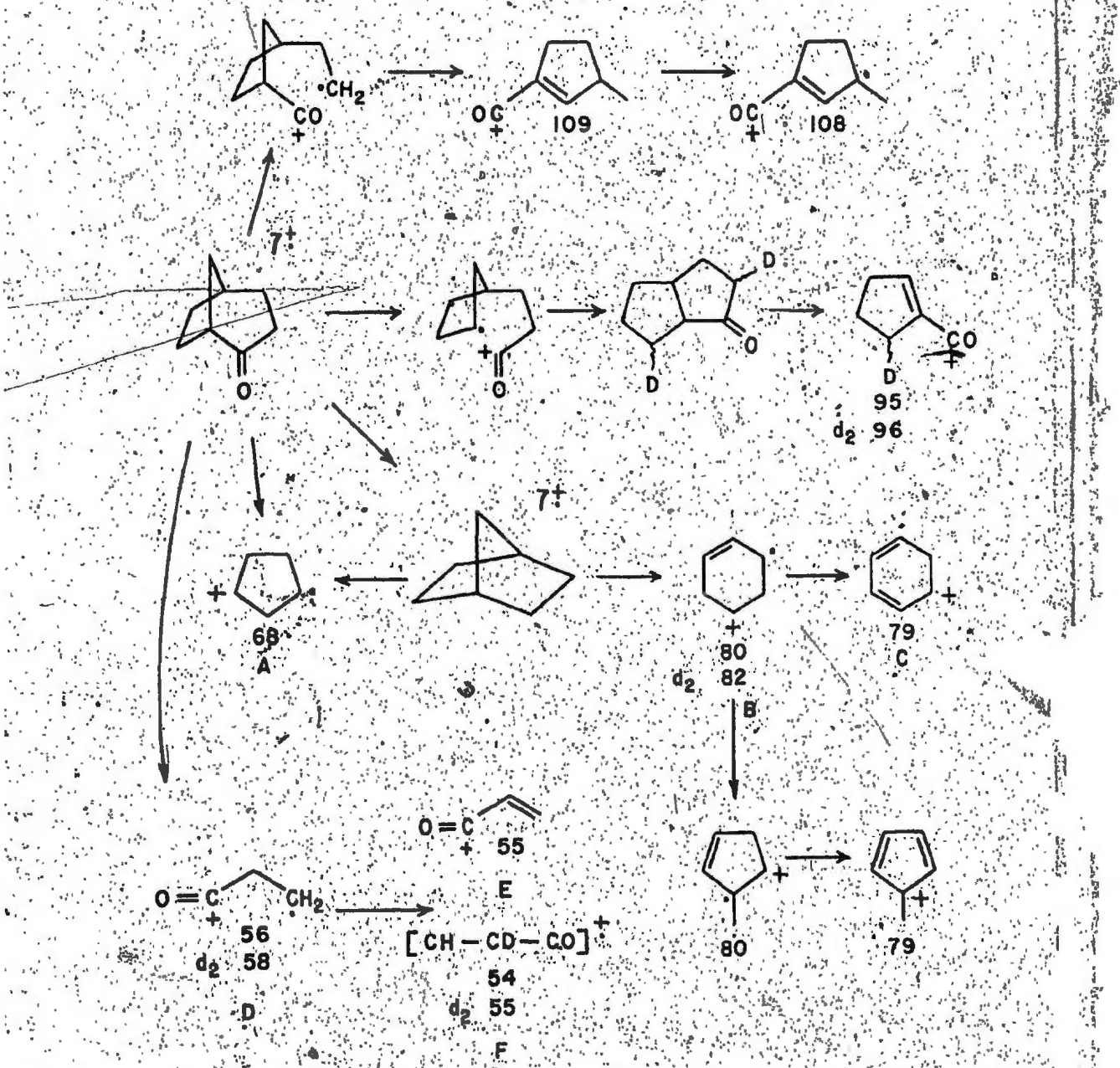
The mass spectra of the unsubstituted ketones (XVII, XXV) display several similarities. Both compounds possess base peaks at m/e 80, attributed to a cyclohexane or methyl cyclopentane fragment, formed by elimination of carbon monoxide from the molecular ion. The mass spectrum of IX displayed peaks at m/e 94, 95 (base peak), 109 and 110, which may be represented by analogous methyl-substituted ions. In contrast, d_2-XXV, possessed a base peak at m/e 91, tentatively regarded as the tropylium ion in the absence of conclusive evid-

ence. The peak at m/e 80 remains, however, comparatively significant in the spectrum of the deuterated compound. The base peaks at m/e 95 and 71 in the spectra of IX and d_2-IX represent major ions in the corresponding spectra. All compounds displayed major peaks at m/e 28, as expected, corresponding to carbon monoxide. A major peak at m/e 88 in the spectrum of d_2-XVII remains unaccounted for and is absent from that of the non-deuterated compound. High resolution spectrometry appears necessary to permit the elucidation of a satisfactory structure.

Bicyclo(3.2.1)octan-2-one (XVII)

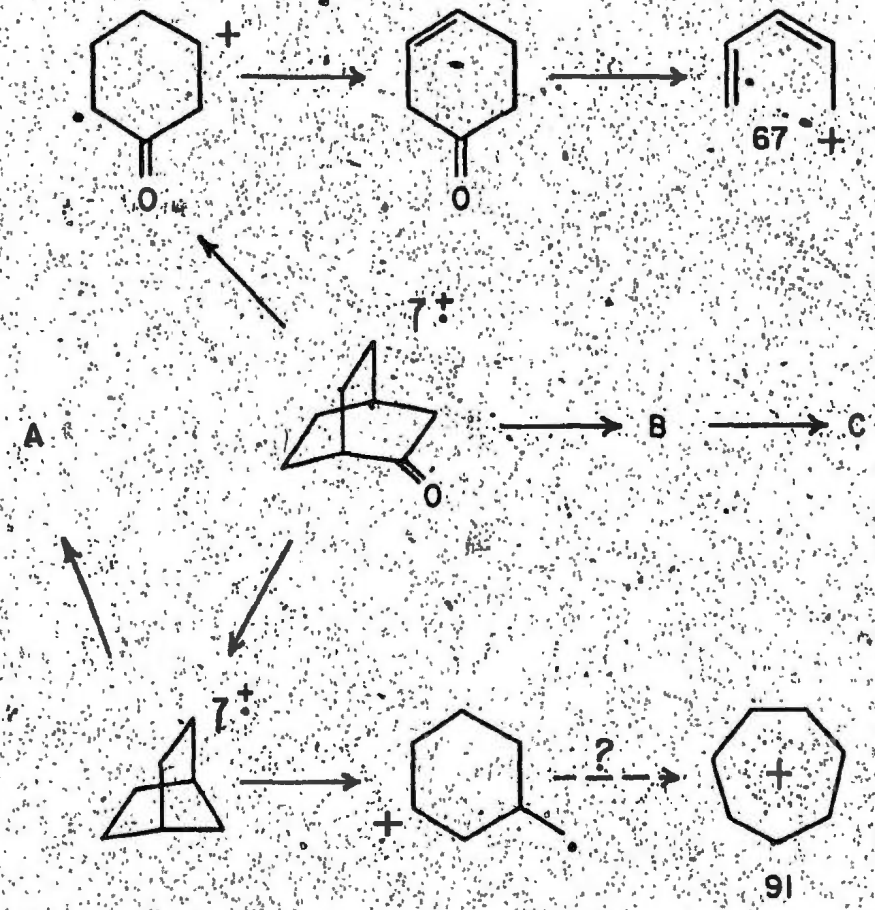
m/e	109	108	95	81	80	79	67	56	41	28
%	56	40	50	33	100	27	90	34	29	11

d_2 m/e	96	95	88	80	79	68	67	58	55	41	28
%	19	13	21	100	11	21	15	19	14	14	21



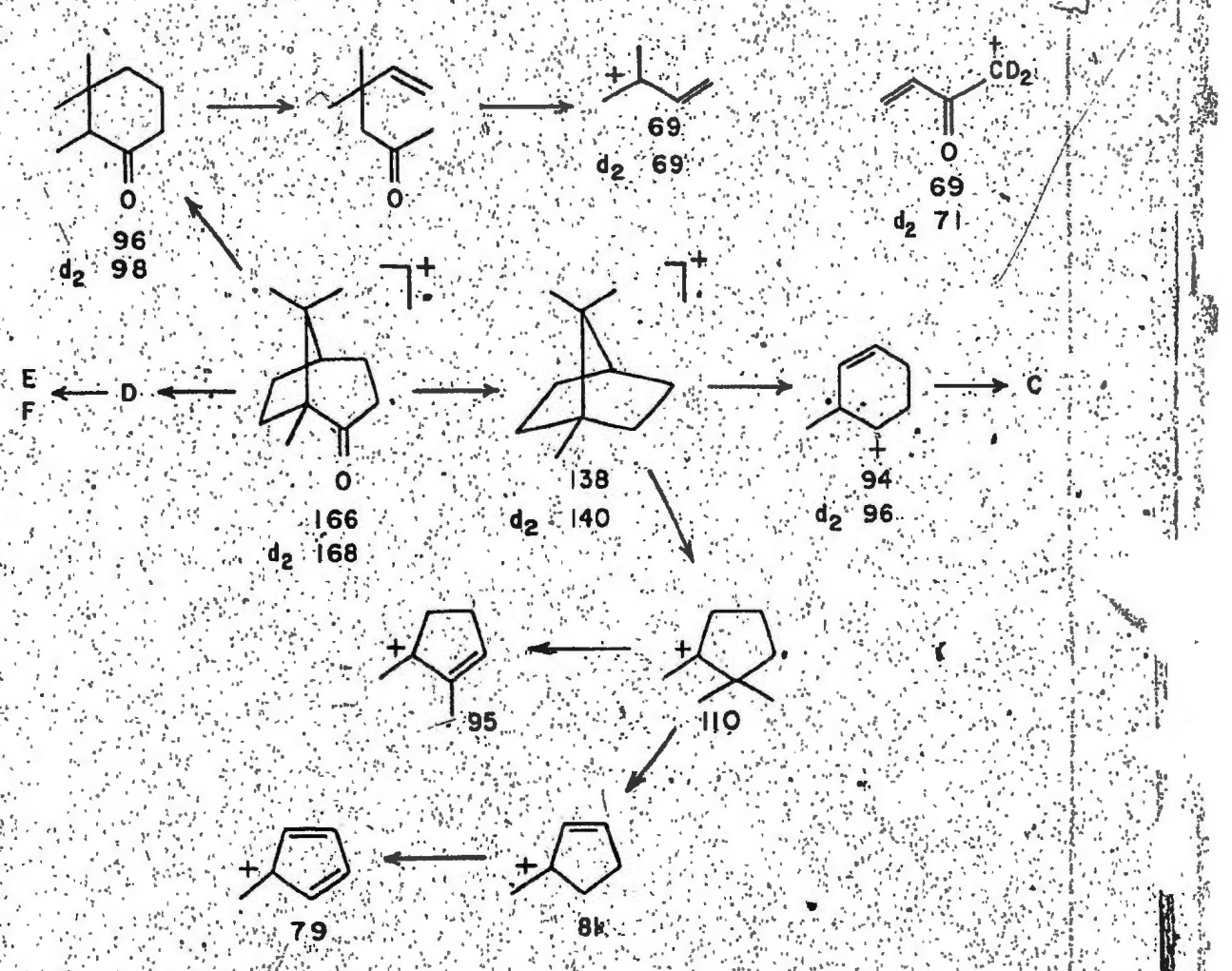
Bicyclo(2.2.2)octan-2-one (XXV)

	m/e	109	91	87	81	80	79	71	67	55	44	43	41	28
	%	21	100	28	21	23	19	26	32	34	27	26	30	32
d_2	m/e	126	83	82	81	80	79	67	55	54	41	28		
	%	88	36	48	76	100	40	66	51	57	37	38		



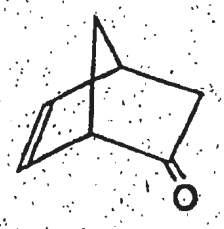
1,8,8-Trimethylbicyclo(3.2.1)octan-2-one (IX)

	m/e	151	138	110	109	108	107	96	95	87	83	82	81
	%	40	7	61	51	26	34	22	100	29	31	21	49
	m/e	69	67	55	43	41	28						
	%	47	30	44	55	55	69						
d_2	m/e	111	109	107	98	95	84	83	81	71	69	66	55	43	28
	%	36	34	29	12	59	37	31	77	100	28	38	33	40	67

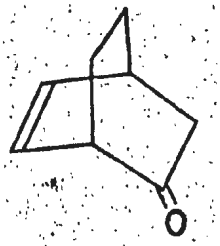


Preparation Of Bicyclooctanones.

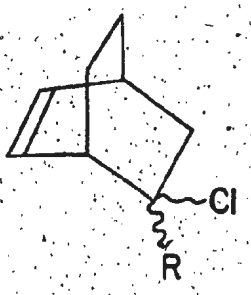
Although bicyclo(2.2.2)octan-2-one (XXV) and its derivatives have previously been synthesized by various other methods,[93,94] the Diels-Alder route has proved the most useful.[95-101] An improved synthesis was sought which would provide the ketone readily and in good yield. In view of the successful preparation by Corey of bicyclo-(2.2.1)hept-5-en-2-one (XXXVII) by Diels-Alder addition of cyclopentadiene and 2-chloroacrylyl chloride,[102] synthesis of the homologous unsaturated ketone (XXXVIII) was anticipated employing that dienophile and cyclohexadiene. Catalytic hydrogenation would provide the desired saturated compound.



XXXVII



XXXVIII



XXXIX

a : R=COCl
b : R=CON$_3$
c : R=N=C=O

An ethereal solution of the diene and 2-chloroacrylyl chloride, the latter prepared from the carboxylic acid and thionyl chloride, was stirred at reflux for two weeks,

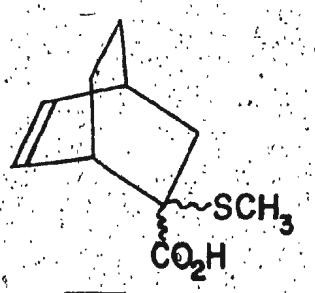
during which time a precipitate formed. After removal of most of the solvent, the adduct (XXXIXa) was stirred at room temperature for eighteen hours with a solution of sodium azide in dimethoxyethane, the precipitate of sodium chloride removed by filteration, and the filtrate containing the acyl azide (XXXIXb) heated at reflux for eight hours to effect Curtius rearrangement to the isocyanate (XXXIXc). The solution was then heated for seven hours with a 2:1 mixture of acetic acid : water, after which it was diluted with water and extracted with petroleum ether. Removal of the solvent provided a yellow oil in 21% yield, shown by g.l.c. analysis to contain one component. The infrared spectrum possessed a band in the carbonyl region at 1712 cm^{-1} typical of a non-conjugated ketone. Two six-line multiplets at δ6.19 and 6.42, representing one proton each, were assigned to the vinyl protons of the structure (XXXVIII).

Attempts to repeat the preparation on a large scale proved unsuccessful. The Diels-Alder step was conducted in benzene and the intermediates isolated at each step of the sequence. In view of the low solubility of sodium azide in dimethoxyethane, a solution of the adduct (XXXIXa) in that solvent was added to an aqueous solution of the salt and the mixture stirred for eighteen hours. Infrared absorption at 2100 and 2140 cm^{-1} was typical of the stretch-

ing vibration of the expected acyl azide.[103] Vigourous heating in diglyme was required to effect rearrangement to the isocyanate (XXXIXc), whose infrared spectrum displayed the characteristic absorption at 2250 cm^{-1}. Treatment with a catalytic amount of acetic acid at room temperature and subsequent workup permitted the isolation of an oil, whose n.m.r. spectrum displayed absorption in the vinyl region at lower field than that required for the bicyclo(2.2.2)octene system. This absorption at δ7.2 remained even after catalytic hydrogenation and is typical of aromatic systems. Possibly, cleavage of the cyclohexanone ring occurs with subsequent aromatization of the remaining six-membered ring.

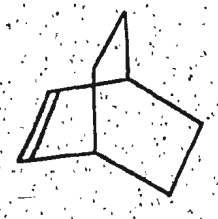
Another possibility involves acid-catalyzed rearrangement of the bicyclo(2.2.2) system to the thermodynamically more stable bicyclo(3.2.1) system, for which there is ample evidence in the literature.[104-107] This explanation is perhaps unlikely in view of the fact that Corey[102] did not observe Wagner-Meerwein rearrangement of the analogous bicyclo(2.2.1) system, shown by solvolysis studies to occur more readily, and in view of the recent publication[108] of an improved synthesis of XXXVIII based on Corey's Diels-Alder preparation, but utilizing the acid-catalyzed decarboxylation of the sulphenylated carboxylic acid (XL). While this explanation remains a possibility, it fails to account

for the presence of vinyl absorption at low field. Satisfactory determination of the nature of the reaction products was not possible and perhaps warrants further investigation, particularly in view of the successful small-scale preparation.



XL

The ketone (XXV) was ultimately synthesized in 46% yield by hydroboration of bicyclo(2.2.2)octene (XLI), based on a paper by Tidwell and coworkers,[109] but which provided no experimental details. The olefin was treated with a suspension of sodium borohydride in tetrahydrofuran, with the addition of boron trifluoride etherate. After

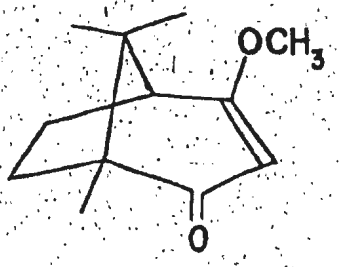


XLI

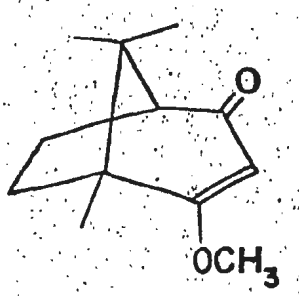
stirring at room temperature for four hours, the resulting borohydride complex was treated with chromic acid to effect

decomposition and oxidation to the ketone. Purification by sublimation gave a crystalline solid, melting at 158-162°C (lit. m.p. 178.5-179°C[97]).

Since homocamphor was previously accessible only by a lengthy sequence involving a tedious separation of the methyl ethers (XLI and XLII), followed by reduction and catalytic hydrogenation,[110-116] the development of a short efficient route to the ketone was of considerable value.



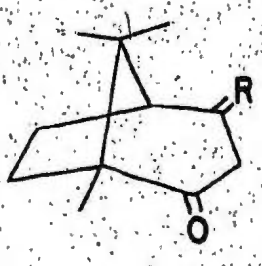
XLI



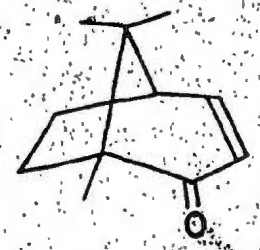
XLII

Examination of a model of homocamphorquinone (XLIIIa), available by hydrolysis of the ethers (XLI and XLII), suggests that the C-2 carbonyl group is sterically hindered due to the presence of the methyl groups and, therefore, should be less susceptible to attack than the more exposed C-4 group. Advantage could be taken of this fact by the choice of a reducing agent which would selectively reduce the less hindered carbonyl while leaving the desired group free from attack. Hydrogenation of the resulting α,β-unsaturated ketone (XLIV) would provide the desired compound.

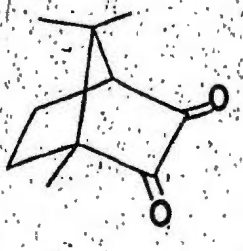
The methyl ethers were prepared by oxidation of camphor (III) and ring expansion of the resulting camphorquinone with diazomethane. Camphor was oxidized according to the method of Evans et. al.[117] A mixture of the ketone and selenium dioxide in acetic acid was heated under reflux for twenty-four hours, after which the resluting elemental selenium was removed by filtration through Celite. The



XLIII



XLIV



XLV

a: R = O
b: R = $NNHSO_3C_6H_4CH_3$
c: R = $NNHCONH_2$
d: R = NNH_2

yellow precipitate obtained after neutralization with potassium hydroxide was recrystallized from methanol to provide bright yellow needles of camphorquinone (XLV), melting at 198-200°C (lit. m.p. 198°C). Infrared absorption at 1770

and 1750 cm^{-1} was attributed to the C-3 and C-2 carbonyl groups, respectively.

Treatment of camphorquinone with an ethereal solution of diazomethane, generated from N-methyl-N-nitroso-p-toluenesulphonamide (Diazald), according to the procedure of Favre and coworkers,[111] and removal of the solvent, afforded a yellow oil, shown by g.l.c. analysis to contain a 1:1 mixture of the ethers. Hydrolysis was effected by stirring an ethereal solution for three days with aqueous hydrochloric acid. Following extraction of the combined organic layers with aqueous sodium hydroxide and reacidification, a white precipitate was filtered and recrystallized from benzene to provide homocamphorquinone (XLIIIa), melting at 220-222°C (lit. m.p. 223-224°C [113]).

Selective reduction of XLIIIa was attempted utilizing sodium bis(2-methoxyethoxy)-aluminum hydride (Red-al), chosen for its greater stability and comparable reducing activity relative to lithium aluminum hydride.[118] A stirred solution of the dione and Red-al in ether-benzene was refluxed for ten hours in a nitrogen atmosphere, and the solid isolated after workup was shown to be the unreacted dione. Repeated attempts failed to detect any reduced material. Use of the less bulky reducing agent, lithium aluminum hydride, also resulted only in the recovery of homocamphor.

In light of the successful reduction of some related bicyclic ketones, by sodium cyanoborohydride reduction of their tosylhydrazones,[119] the selective reduction of homocamphor was anticipated. The difficulty experienced in reducing such sterically hindered ketones as d-camphor and fenchone suggested that the C-2 carbonyl would be protected from attack. A solution of equimolar amounts of the dione and tosylhydrazide in aqueous methanol was permitted to stand for eighteen hours at room temperature and the resulting precipitate filtered and recrystallized from methanol to afford a crystalline solid, melting at 220-222°C. A molecular ion peak at m/e 348 indicated the product was the monotosylhydrazone (XLIIIb).

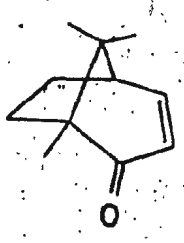
A mixture of the tosylhydrazone and a four-fold excess of sodium cyanoborohydride in 1:1 sulpholane : dimethylformamide was refluxed for five hours. The oil obtained after dilution with water and extraction with cyclohexane lacked infrared absorption in the NH, OH and C=O regions and a hydrocarbon product is speculated. Attempted *in situ* formation of the tosylhydrazone and reduction catalyzed by a small amount of p-toluenesulphonic acid resulted in the recovery of the dione. Use of a ten-fold excess of reducing agent and careful maintaining of the pH below 3.8 with concentrated hydrochloric acid produced a complex mixture which appeared to contain unreduced tosylhydrazone.

A method utilizing Wolff-Kishner reduction, developed by Barton[120] for the reduction of sterically hindered ketones, was employed. Attempted reduction by *in situ* formation of the hydrazone (XLIIId) in a solution of the dione in diethylene glycol, containing hydrazine hydrate and solid potassium hydroxide,[121] resulted in recovery of the dione and unreduced hydrazone.

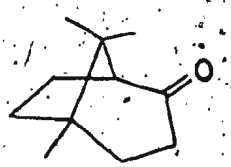
Subsequently, an attempt was made to reduce the semicarbazone derivative (XLIIIc), prepared by heating an aqueous methanolic solution of equimolar quantities of the dione and semicarbazide hydrochloride in the presence of a small amount of pyridine. The resulting precipitate was filtered and recrystallized from aqueous ethanol to give a crystalline solid, melting at 230-231°C. A molecular ion peak in the mass spectrum at m/e 237 indicated the monosemicarbazone, as expected due to steric hinderance of the C-2 carbonyl group. Bands at 1690 and 1700 cm^{-1} in the infrared spectrum of the nujol mull were assigned to the semicarbazone and ketone carbonyls, respectively.

A solution of XLIIIc and solid potassium hydroxide in dimethylsulphoxide and diethylene glycol (4:1)[122] was stirred at 130-180° for five hours, and the oil obtained after dilution with water and extraction with cyclohexane was shown by g.l.c. analysis to be a mixture. Bands at

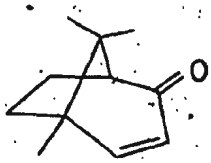
1708 and 1675 cm^{-1} in the infrared spectrum suggested the presence of the α,β-unsaturated ketone (XLVI). Variations in the reaction temperature and base concentration resulted in the formation of a complex mixture.



XLVI



XLVII



XLVIII

In light of the successful reduction of ketones which previously gave abnormal products in the standard Wolff-Kishner reaction, by the use of strong base and elevated temperatures,[123] a solution of XLIIIc and potassium t-butoxide in toluene and 2-propanol was prepared. G.l.c. analysis failed to detect any reduced product after refluxing for three days. When the semicarbazone was refluxed for one and one half hours in the higher boiling solvents, p-xylene and 1-pentanol (1:1), and three molar equivalents of the base, followed by

dilution with water and washing with a small amount of dilute acetic acid, an oil was obtained in 35% yield. On the basis of a molecular ion peak at m/e 164, the product appeared to be the α,β-unsaturated ketone (XLVI), rather than homocamphor as expected. Careful monitoring by g.l.c. and rapid workup on completion of the reaction was required to prevent the formation of a compound at the expense of the reduced product. A sample of the unknown, obtained by preparative g.l.c., appeared to be quite polar on the basis of a large retention time (Column A), and possessed a molecular ion peak at m/e 182 in its mass spectrum. Further work is required to determine the reaction conditions necessary for optimum yields.

Ultimately, homocamphor and its isomer, homoepicamphor (XLVII), were prepared by a synthesis employed by Baker and Davis[112], involving lithium aluminum hydride reduction of the methyl ethers (XLI and XLII), and subsequent hydrogenation of the resulting α,β-unsaturated ketones (XLVI and XLVIII).

A suspension of the methyl ethers and lithium aluminum hydride in anhydrous diethyl ether was refluxed for two hours, and the resulting complexes stirred with sulphuric acid to effect decomposition. The yellow oil obtained after extraction with ether had a strong smell of camphor and displayed absorption at 1710 and 1680 cm^{-1}

in the infrared spectrum. A doublet of doublets at δ6.98 and a doublet at δ5.79 (J=9 cps) in the n.m.r. spectrum, were assigned to the vinyl protons of XLVI, while doublets at δ6.65 and 5.77 (J=10 cps) were attributed to the vinyl protons of the isomer, XLVIII.

An ethanolic solution of the unsaturated ketones, containing platinum oxide and a small amount of pyridine, was hydrogenated. Filtration through Celite and removal of the solvent afforded an oil, which possessed carbonyl absorption at 1708 cm^{-1}, and lacked absorption in the n.m.r. spectrum due to the vinyl protons. G.l.c. analysis indicated a 1:1 mixture of homocamphor and homoepicamphor.

Separation of the isomers was anticipated by removal of homoepicamphor as its semicarbazone derivative. Steric crowding of the carbonyl group of homocamphor by the methyl groups should impede attack by the nucleophilic semicarbazide. A solution of the ketones in methanol, containing 0.5 molar equivalent of aqueous semicarbazide solution and a small amount of pyridine,[124] was heated gently for ten minutes. The precipitate which formed on cooling was filtered and washed successively with water and benzene to provide a solid, which melted at 207-211°C.

Homocamphor was isolated by acidification of the filtrate and extraction with diethyl ether. Purification alternatively by preparative g.l.c. (Column A), or by

thin layer chromatography on fluorescent silica gel, eluting with 10% ether-petroleum ether, provided crystalline material which melted at 178-179°C (lit. m.p. 187-190°C[111]). The mass spectrum contained a molecular ion peak at m/e 166. Infrared absorption in the carbonyl region at 1706 cm^{-1}, and singlets at δ0.79, 0.85 and 0.88, due to the C_9, C_{10} and C_{11} methyl groups, respectively, provided confirmation that the compound was homocamphor.

The remaining ketone, bicyclo(3.2.1)octan-2-one (XVII), was readily available commercially (Aldrich).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus or with a Thomas-Hoover "Uni-Melt" apparatus and are uncorrected. Elemental microanalyses were performed by Alfred Bernhardt, West Germany.

Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrometer, and were calibrated against the 2850 and 1601 cm^{-1} bands of polystyrene film. Nuclear magnetic resonance spectra were determined with a Varian Model A-60, Varian Model EM-360 or Varian HA-100 spectrometer; Band positions are reported in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer Model RMU-6E mass spectrometer at an ionization potential of 70eV unless otherwise specified.

Gas liquid chromatographic analyses were conducted on a Varian Aerograph Model 1720 gas chromatograph using helium as the carrier gas. Column A refers to a 8' x 1/4", 13% SE-30 column supported on Chromosorb W (AW-DMCS) (70-80 mesh); Column B refers to a 8' x 1/4", 20% Carbowax 20M column supported on Chromosorb W (AW-DMCS) (70-80 mesh).

Irradiations were carried out in stoppered Pyrex containers, using a water-cooled Hanovia 450-watt medium pressure mercury arc lamp, on solutions (ca. 0.01M) which had been thoroughly flushed with nitrogen.

Organic solutions were dried over anhydrous magnesium sulphate and evaporated by means of a Buchi rotary evaporator under reduced pressure. With the exception of methanol, most organic solvents were dried and distilled from sodium wire; absolute methanol was distilled from magnesium. In certain cases spectrophotometric solvents were used without further purification.

The Photochemistry of Some Bicyclooctanones

Photolysis of Bicyclo(3.2.1)octan-2-one (XVII).

(i) In Methanol:

A solution of bicyclo(3.2.1)octan-2-one (0.150g, 0.0012 mole) in absolute methanol (13 ml), to which sodium bicarbonate (0.040 g) had been added, was irradiated for six hours. After removal of the solvent, carbon tetrachloride was added, the solution filtered and concentrated to yield a colourless oil. G.l.c. analysis (Column A, 140°) revealed two major peaks in a ratio of 9:1. Analysis on Column B allowed a resolution of the principal peak into two components in a ratio of 7:2 (XVIII : XIX). The alde-

hydic products, XVIII and XIX, were separated by preparative g.l.c. (Column B, 207°). The major product had the following spectral properties:

I.r. (CCl_4): 2810 (CHO), 2705 (CHO), 1725 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ9.74 (t, J=2 cps, 1 H), 5.63 (m, 2 H), 2.85-1.0 (complex, 9 H) ppm.

N.m.r. (d_6-benzene); δ1.0-2.7 (complex, 9 H), 5.53 (m, 2 H), 9.25 (br, 1 H) ppm.

N.m.r. (CCl_4 + $Eu(fod)_3$): δ9.72 (t, J=7 cps, 2 H), 6.68 (m, 1 H), 6.37 (d of d, J=6 cps, 2 H), 5.50 (m, 1 H), 5.07 (br m, 1 H), 4.10 (t, J=7 cps, 1 H), 3.88 (d, J=6 cps), 3.3-1.9 (complex) ppm.

Preparation of the Semicarbazone of 3-(2'-cyclopentenyl)propionaldehyde (XVIII).

A solution of semicarbazide hydrochloride (0.100 g, 0.0088 mole) and sodium acetate (0.075 g, 0.0092 mole) in water (5 ml) was added dropwise with shaking to the unsaturated aldehyde (0.050 g, 0.40mmole) and 95% ethanol (5 ml) added. The clear solution was warmed gently for a few minutes on a steam bath, cooled and water added until a precipitate formed, filtered to yield a solid (0.036 g, 50%). Recrystallization from ethanol-water provided needles, m.p. 126-126.5°C.

Anal. Calcd. for $C_9H_{15}ON_3$: C, 59.63; H, 8.35; N, 23.19.

Found: C, 59.65; H, 8.16; N, 23.37.

The minor aldehyde (XIX), collected by preparative g.l.c. as a colourless oil, had the following spectral properties:

I.r. (CCl_4): 3100 (CH), 1725 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ9.75 (t, J=2 cps, 1 H, CHO), 5.55 (s, 2H, CH=CH), 2.75-0.9 (complex, 9H) ppm.

N.m.r. (d_6-benzene): δ0.9-2.7 (complex, 9H), 5.58 (br s, 2H), 9.70 (br s, 1H) ppm.

Preparation of the Semicarbazone of 3-(3'-cyclopentenyl)propionaldehyde (XIX):

A solution of semicarbazide hydrochloride (0.050 g, 0.0044 mole) and sodium acetate (0.075 g, 0.00092 mole) in water (3-4 drops) was added to the aldehyde (0.023 g, 0.19 mmole) and 95% ethanol added dropwise with shaking until the solution became clear. After heating gently for ten minutes on a steam bath, the solution was cooled and a white precipitate collected by filtration. Recrystallization from ethanol-water provided a solid (0.009 g, 25%), melting at 123-123.5°.

Anal. Calcd. for $C_9H_{15}ON_3$: C, 59.63; H, 8.35; N, 23.19.

Found: C, 59.55; H, 8.43; N, 23.34.

(ii) In Tetrahydrofuran : Water:

A solution of bicyclo(3.2.1)octan-2-one (8.0 g, 0.064

mole) in a 1:1 mixture of THF : water (640) was irradiated until g.l.c. analysis indicated the photolysis was 85% complete. The solution was extracted twice with diethyl ether, the combined organic layers washed with aqueous 10% sodium bicarbonate solution and water until the washings were neutral, dried and concentrated to give a mixture of isomeric aldehydes, XVIII and XIX, and starting ketone as a colourless oil (6.2 g, 78%). G. l.c. analysis showed the aldehydes to be present in a ratio of 8:2 (XVIII : XIX).

When a portion of the irradiation mixture was photolyzed for a further twenty hours, g.l.c. analysis indicated that the peak corresponding to the aldehydes had diminished in intensity. Preparative g.l.c. permitted the isolation of a new compound which eluted at shorter retention time and which had the following spectral properties:

I. r. (CCl_4): 1460-1160 (m-s, C-O) $cm.^{-1}$

N.m.r. (CCl_4): δ1.0-2.5 (complex, 9H), 2.8 (m, 2H), 3.9 (complex m, 2H) ppm.

3-Cyclopentylpropionic Acid (XXa):

The combined aqueous layers obtained from the irradiation mixture were acidified with 6N hydrochloric acid and extracted twice with ether. The organic phase was

then washed with water until the washings were neutral, dried and concentrated to yield a colourless liquid (0.6 g, 7.5%), whose spectral properties matched those of an authentic sample of 3-cyclopentylpropionic acid (Aldrich).

I.r. (CCl_4): 3510 (sh, OH), 3400=3050 (b, OH), 2750-2550 (b, OH), 1708 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ10.13 (broad s, 1 H), 2.8-0.9 (complex, 13 H) ppm.

Methyl 3-Cyclopentylpropionate (XXb):

An ethereal solution of the carboxylic acid (XXa) was treated at 0° with a solution of diazomethane in diethyl ether until the yellow colour persisted. After standing for a few minutes, the solvent was removed under reduced pressure to yield the ester (XXb) as a colourless oil with a sweet fruity odour.

I.r. (CCl_4): 1738 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ1.0-2.6 (complex), 3.60 (s, $COOCH_3$) ppm.

A sample of methyl 3-cyclopentylpropionate was prepared from authentic 3-cyclopropionic acid, according to the method described above, and possessed identical spectral properties.

Silver Oxide Oxidation of Isomeric Aldehydes (XVIII and XIX): Preparation of 3-(2'-Cyclopentenyl)- and 3-(3'-Cyclopentenyl)propionic Acids and Isolation of Methyl 3-Cyclopentylpropionate (XXb):

To a stirred dioxane solution (5 ml) of the methanolic irradiation mixture (0.500 g, 0.004 mole) was added a solution of silver nitrate (0.350 g, 0.002 mole) and sodium hydroxide (0.8 g, 0.02 mole) in water (7 ml) at 0°. The reaction was stirred for a further 27 hours at room temperature, filtered, and the residue washed several times with hot water.

The basic filtrate was extracted with diethyl ether (twice), the combined ethereal layers washed with water until the washings were neutral, dried, filtered and concentrated to provide the ester (XXb) as a colourless oil (0.042 g, 7.5%).

I.r. (CCl_4): 1738 cm^{-1}.

N.m.r. (CCl_4): δ0.9-2.6 (complex), 3.60 (s) ppm.

The combined aqueous layers were acidified with 6N hydrochloric acid and extracted with ether (twice). The combined organic layers were washed with water until the washings were neutral, dried, filtered and concentrated to give the acids as a colourless oil (0.500 g, 89%). G.l.c. analysis indicated a complete absence of aldehydes.

I.r. (CCl_4): 3600-3200 (br, OH), 1705 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ10.47 (s, COOH), 5.68 (br s, CH=CH), 2.7-1.0 (complex) ppm.

Hydrogenation of 3-(2'-Cyclopentenyl)- and 3-(3'-Cyclopentenyl)propionic Acids: Formation of 3-Cyclopentylpropionic Acid (XXa):

A solution of the unsaturated acids obtained above (0.083 g, 0.0006 mole) in ethyl acetate (20 ml), to which 5% palladium on carbon (0.040 g) had been added, was hydrogenated at room temperature and atmospheric pressure. The mixture was filtered through Celite and concentrated to provide a pale yellow oil (0.069 g, 83%).

I.r. (CCl_4): 3520 (sh), 3500-3100 (br), 2700-2500 (br), 1705 cm^{-1}.

N.m.r. (CCl_4): δ2.5-0.9 (complex), 12.2 (s) ppm.

Ozonolysis and Methylation of 3-(2'-Cyclopentenyl)- and 3-(3'-Cyclopentenyl)propionic Acids: Formation of Dimethyl 4-Carbomethoxyheptane-1,7-dioate and Dimethyl 3-(carbomethoxymethyl)pentane-1,5-dioate (XXIb, XXIIb):

A solution of the mixture of unsaturated carboxylic acids obtained above in 1:1 methanol : dichloromethane was prepared in a 3-necked round-bottomed flask. After treatment at -78° with a stream of oxygen containing ozone (approx. 6%) until the solution retained a blue colour,

it was allowed to reach room temperature, aqueous 30% hydrogen peroxide solution (0.35 ml, 0.0041 mole) was added and the solution stirred for eighteen hours. An ethereal solution of diazomethane was then added at 0° until the yellow colour persisted and the solvent removed under reduced pressure. Extraction with ether (twice), followed by washing the combined extracts with water, drying, filtering and concentrating the solution provided a colourless oil (0.181 g, 91%).

I.r. (CCl_4): 1745, 1740 cm^{-1}.

N.m.r. (CCl_4): δ3.63 (s, 6 H), 3.43 (s, 3 H), 3.83 (s), 3.65 (s), 2.8-1.0 (complex) ppm.

Dimethyl 4-carbomethoxyheptane-1,7-dioate (XXIb) was prepared by the addition of an ethereal solution of diazomethane at 0° to a sample of authentic carboxylic acid (XXIa) (Aldrich), and the spectral properties matched those of the major ozonolysis product.

(iii) In Diethyl Ether:

A solution of bicyclo(3.2.1)octan-2-one (0.250 g, 0.002 mole) in diethyl ether (6 ml), containing cyclohexylamine (0.3 ml), was irradiated for twelve hours. The solvent was removed under reduced pressure, the residue dissolved in chloroform and washed with dilute hydrochloric acid and water until the washings were neutral. After

drying and filtering, the solution was concentrated to provide a pale brown oil (0.240 g, 96%). G.l.c. analysis indicated the reaction was approximately 10% complete. Calculation of the relative intensities of the n.m.r. signals provided an approximate ratio for aldehyde : ketene of 1:2.5.

I.r. ($CHCl_3$): 2850 (CHO), 1715 (v br, C=O) cm^{-1}.

N.m.r. ($CDCl_3$): δ2.8-1.0 (complex), 4.3 (br s, NH), 5.6 (br s, CH=CH), 9.7 (br s, CHO) ppm.

Photolysis of Bicyclo(2.2.2)octan-2-one (XXV):

(i) In Methanol:

A solution of bicyclo(2.2.2)octan-2-one (0.200 g, 0.0016 mole) in absolute methanol (20 ml), to which sodium bicarbonate (0.020 g) had been added, was irradiated for four hours. After removal of the solvent and addition of petroleum ether, the solution was filtered and concentrated to afford a colourless oil (0.200 g, 100%). G.l.c. analysis indicated essentially complete reaction of the ketone. Comparison of aldehyde and methoxyl peaks of the n.m.r. spectrum indicated an aldehyde : ester ratio of approximately 4:1.

I.r. (CCl_4): 2825 (CHO), 2700 (CHO), 1735 (C=O, ester), 1725 (C=O, ald.) cm^{-1}.

N.m.r. (CCl_4): δ9.68 (t, J=1.5 cps, CHO), 5.60 (br s, CH=CH), 3.62 (s, $COOCH_3$) ppm.

Silver Oxide Oxidation of 3-Cyclohexenylacetaldehyde (XXVI): Isolation of Methyl Cyclohexylacetate (XXVIIb) and Formation of 3-Cyclohexenylacetic Acid (XXVIIIa).

To a solution of silver nitrate (0.0170 g, 0.001 mole) and sodium hydroxide (0.080 g, 0.002 mole) in water (3 ml). After stirring at room temperature for 1.5 hours, the solution was filtered, the residue washed several times with hot water and the filtrate extracted with ether (twice). The combined organic extracts were washed with water, dried, filtered and concentrated. The methyl ester (XXVIIb) was isolated as a colourless oil (0.045 g, 36%).

I. R. (CCl_4): 1735 cm^{-1}.

N.m.r. (CCl_4): δ3.60 ($COOCH_3$, s), 1.1-2.6 (complex) ppm.

The combined aqueous layers were acidified with 6N hydrochloric acid and extracted with ether (twice), the ethereal layers combined and washed with water (several times), dried, filtered and concentrated to yield the unsaturated carboxylic acid (XXVIIIa) as a colourless oil (0.075 g, 53.5%).

I.r. (CCl_4): 3500 (sh, weak, OH), 3400-3100 (br, OH), 2750-2550 (OH), 1710 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ1.1-2.5 (complex), 5.57 (s, CH=CH), 11.77 (s, COOH) ppm.

Hydrogenation of 3-Cyclohexenylacetic Acid (XXVIIIa) to Formation of 3-Cyclohexylacetic Acid (XXVIIa).

A solution of the carboxylic acid (0.050 g, 0.35 mmole) in ethyl acetate (20 ml) was hydrogenated in the presence of 5% palladium on carbon (0.020 g). The solution was filtered through Celite and the filtrate concentrated to afford a colourless oil (0.048 g, 95%).

I.r. (CCl_4): 3500-3100, 2750-2500 (br, OH), 1710 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ1.0-2.6 (complex), 12.0 (s, COOH) ppm.

(ii) In Tetrahydrofuran : Water:

A solution of bicyclo(2.2.2)octan-2-one (0.278 g, 0.0022 mole) in a 1:1 mixture of THF : water (22 ml) was irradiated for seven hours and extracted with ether (twice). The combined extracts were washed with aqueous 10% sodium bicarbonate solution (twice) and water, dried, filtered and concentrated to provide the aldehyde as an oil (0.243 g, 87.5%).

I.r. (CCl_4): 2810 (CH), 2700 (CH), 1725 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ1.0-2.4 (complex), 5.57 (br s, 2 H, CH=CH), 9.63 (t, J=2 cps, 1 H, CHO) ppm.

The combined aqueous layers were acidified with 6N hydrochloric acid and extracted with ether (twice). The

combined ethereal layers were washed with water until the washings were neutral, dried, filtered and concentrated to yield an oil (0.013 g, 4.15%).

I.r. (CCl_4): 3500 (sh, OH), 3400-3100 (br, OH), 1705 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ1.3-2.8 (complex), 5.60 (s, 2 H), 11.35 (br s, 1 H) ppm.

Preparation of Methyl 3-Cyclohexenylacetate (XVIIIb).

An ethereal solution of 3-cyclohexenylacetic acid (0.050 g, 0.0004 mole) was treated at 0° with a solution of diazomethane in ether until the yellow colour persisted. Removal of the solvent under reduced pressure afforded the ester as a pale yellow oil (0.055 g, 100%).

I.r. (CCl_4): 1735 cm^{-1}.

N.m.r. (CCl_4): δ1.2-2.7 (complex), 3.63 (s, $COOCH_3$), 5.60 (br s, CH=CH) ppm.

Photolysis of 1,8,8-Trimethyl(3.2.1)octan-2-one (Homocamphor) (IX).

(i) In Methanol:

A solution of homocamphor (0.055 g, 0.00032 mole) in absolute methanol (3.5 ml) containing sodium bicarbonate (0.010 g) was irradiated for seven hours. After

evaporation of the solvent and the addition of petroleum ether, the solution was filtered and concentrated to yield a colourless oil (0.054 g, 99%), shown by g.l.c. analysis to be a mixture of two new components (ratio 4:1) in addition to the starting ketone (approx. 10%). Examination of the n.m.r. spectrum indicated a ratio for aldehdye : ester of approximately 4:1.

I.r. (CCl_4): 2870 (CHO), 1740 (C=O, ester), 1725 (C=O, ald.), 1710 (C=O, ket.) cm^{-1}.

N.m.r. (CCl_4): δ0.80, 0.83, 0.90 and 1.0 (s's, Me's), 1.2-2.6 (complex), 3.60 (s, OCH_3), 5.15 (m, vinyl proton), 9.67 (t, J≈1.5 cps, CHO) ppm.

(ii) In Tetrahydrofuran : Water:

A solution of homocamphor (0.035 g, 0.0002 mole) in 1:1 THF : water (2 ml) was irradiated for four hours. After extraction with diethyl ether (twice), the combined extracts were washed with aqueous 10% sodium bicarbonate solution (twice), then water until the washings were neutral, dried, filtered and concentrated to afford a colourless oil (0.028 g, 80%), shown by g.l.c. analysis to be a mixture of aldehyde and starting ketone.

I.r. (CCl_4): 2870 (CHO), 2710 (CHO), 1725 (C=O, ald.), 1710 (C=O, ket.) cm^{-1}.

N.m.r. (CCl_4): δ0.75-2.4 (complex), 5.08 (m, vinyl proton), 9.64 (t, J≈1.5 cps, CHO) ppm.

Acidification of the combined aqueous phases with 6N hydrochloric acid, followed by extraction with diethyl ether (twice), washing the combined extracts with water until the washings were neutral, drying, filtering and concentrating provided the carboxylic acid (XXIXa) (0.0078 g, 2.1%) as a colourless oil.

I.r. (CCl_4): 3500-3100 (br, OH), 2750-2400 (br, OH), 1708 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ0.66, 0.77 and 0.95 (s's,,9 H, Me's), 1.0-2.8 (complex), 12.0 (br, COOH) ppm.

(iii) In Diethyl Ether:

A solution of homocamphor (0.025 g, 0.00015 mole) in diethyl ether (0.5 ml) containing cyclohexylamine (25 µl) was irradiated for seventy-two hours, during which time a precipitate formed. G.l.c. analysis and n.m.r. spectroscopy indicated the absence of aldehyde formation. The solution was filtered and the filtrate washed with 2N hydrochloric acid to remove residual amine, followed by aqueous 10% sodium bicarbonate solution and water until the washings were neutral. The pale yellow oil obtained after filtration of the dried solution appeared to contain mainly the unreacted ketone, on the basis of g.l.c. analysis and the n.m.r. spectrum.

Filteration of the precipitate formed during the photolysis, followed by washing with dilute hydrochloric acid and benzene, and recrystallization from chloroform afforded a crystalline solid, melting at 206-207.5°C. The product was soluble in methanol and ethanol, and insoluble in chloroform, carbon tetrachloride, benzene, ether, petroleum ether and ethyl acetate. The mass spectrum displayed peaks at m/e 99, 70, 56 (base peak), 43 and 30.

I.r. ($CHCl_3$): 3500-3200 (weak), 1705 cm^{-1}.

N.m.r. ($CDCl_3$): δ0.8-2.3 (complex), 3.1 (br, 1 H), 7.9 (br, 2 H) ppm.

The oil obtained from the irradiation was photolyzed for a further ten hours in a 1:1 mixture of THF : ether (2 ml), containing cyclohexylamine (0.5 ml). After workup, as decribed above, the resulting yellow oil (0.012 g, 48%) appeared to contain a mixture of the unreacted ketone, unsaturated aldehyde and cyclohexylamide.

I.r. (CCl_4): 3425-3150 (NH), 1728 (C=O, ald.), 1710 (C=O, ket.), 1675 (C=O, amide) cm^{-1}.

The Preparation of Bicyclooctanones.

Bicyclo(2.2.2)octan-2-one (XXV).

Preparation of 2-Chloroacrylyl Chloride.

Thionyl chloride (30 ml, 0.44 mole) was poured slowly through the top of a condenser connected to a flask containing 2-chloroacrylic acid (20 g, 0.21 mole, Willow Brook Labs). The condenser was fitted with a calcium chloride drying tube and the mixture stirred at reflux for eighteen hours. Distillation (50-60°C) using a water aspirator (~15 mm) afforded a pale yellow oil (14.8 g, 55%).

I.r. (CCl_4): 1748 cm^{-1}.

Preparation of Bicyclo(2.2.2)oct-5-en-2-one (XXXVIII).

A solution of 1,3-cyclohexadiene (1.6 g, 0.020 mole, Aldrich) and 2-chloroacrylyl chloride (2.5 g, 0.020 mole) in anhydrous diethyl ether (20 ml) was carefully prepared in a nitrogen dry box. The reaction was kept in a cold room (~5°C) for two days, then at room temperature for two weeks, and the ether removed by bubbling nitrogen through the solution. A solution of sodium azide (1.3 g,

0.020 mole) in anhydrous dimethoxyethane was added and the mixture stirred for eighteen hours at room temperature. After filtration, the filtrate was heated at reflux for eight hours, by which time the colour had changed from yellow to dark brown. The solution was then treated at 0° with 2:1 acetic acid : water (10 ml) and refluxed for seven hours, the organic solvents removed under reduced pressure ($25-30^{\circ}$), and the residual brown gummy tar treated with water and extracted with petroleum ether. The solution was dried, filtered and concentrated to yield a yellow oil (0.50 g, 21%). G.l.c. analysis (Column A, 140°) indicated only one major component.

I.r. (CCl_4): 1712 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ1.2-2.3 (complex, 8 H), 6.15 (t of d, AMX system, $J_{AM}=J_{AX}\simeq 7$ cps, $J_{MX}=$ 1.5-2.0 cps), 6.42 (t of d, AMX system, $J_{AM}=J_{AX}\simeq 7$ cps, $J_{MX}=$ 1.5-2.0 cps) ppm.

Preparation of Bicyclo(2.2.2)octan-2-one (XXV).

Powdered sodium borohydride (0.60 g, 0.016 mole) was suspended in dry tetrahydrofuran (40 ml) and bicyclo-(2.2.2)oct-2-ene (5.4 g, 0.05 mole, Chem. Sample Co.) added. Boron trifluoride etherate (2.9 g, 0.021 mole) was added dropwise to the stirred mixture over one hour. Stirring was continued for a further three hours at

room temperature and dichromate oxidizing agent (prepared from $K_2Cr_2O_7$ (11 g), H_2SO_4 (8 ml), H_2O (45 ml)) added dropwise until the resulting green solution assumed a yellow tone. After stirring for a further hour at room temperature, the reaction mixture was poured onto ice, extracted with ether, and dried. The residual solid obtained after filtration and removal of the solvent was purified by sublimation (50°/15mm) to give the ketone (2.48 g, 46%), m.p. 158-162°C (lit. m.p. 178.5-179°C[103]).

I.r. (CCl_4): 1710 cm^{-1}.

N.m.r. (CCl_4): δ0.9-2.5 (complex) ppm.

1,8,8-Trimethylbicyclo(3.2.1)octan-2-one (Homocamphor) (IX).

Selenium Dioxide Oxidation of Camphor (III):[117] Formation of Camphorquinone (XLV).

A mixture of camphor (30 g, 0.20 mole) and selenium dioxide (36 g, 0.32 mole) in acetic anhydride (30 ml) was stirred at reflux for twenty-four hours, cooled, filtered through Celite and the residue washed with glacial acetic acid. The filtrate was neutralized with aque-

ous potassium hydroxide solution, and the yellow precipitate filtered and washed with water until the washings were neutral. After drying for several hours in a vacuum dessicator, the crude product was dissolved in benzene and filtered through Celite to remove residual selenium. The solvent was removed under reduced pressure and the product recrystallized from absolute methanol to afford bright yellow needles (29 g, 88%), melting at 198-200°C (sealed tube), (lit. m.p. 198°C[117]). The mass spectrum displayed a molecular ion peak at m/e 152.

I.r. (CCl_4): 1770, 1750 (C=O) cm^{-1}.

N.m.r. (CCl_4): δ1.13 (s, 6 H), 0.92 (s, 3 H), 1.5-2.2 (complex, 4 H), 2.51 (br t, 1 H) ppm.

Ring Expansion of Camphorquinone (XLV):[111,113] Formation of 1,8,8-Trimethyl- and 5,8,8-Trimethyl-4-methoxybicyclo(3.2.1)oct-3-en-2-one (XLI, XLII).

A solution of diazomethane (approx. 0.1 mole, generated from Diazald) in diethyl ether (300 ml) was added dropwise with stirring to a solution of camphorquinone (5.0 g, 0.0030 mole) at 0°. The procedure was repeated until g.l.c. analysis (Column A, 187°) indicated the reaction was complete. Removal of the solvent under reduced pressure afforded a yellow oil (5.9 g, 100%),

shown by g.l.c. analysis to contain approximately a 1:1 mixture of the two components.

I.r. (CCl_4): 1660, 1655, 1615 cm^{-1}.

N.m.r. (CCl_4): δ0.95, 0.97 and 1.09 (3 s, 9 H), 1.2-2.4 (complex, 5 H), 3.70 (s, 3 H), 5.08 (br s, 1 H) ppm.

Lithium Aluminum Hydride Reduction of Methyl Ethers, XLI and XLII: Formation of 1,8,8- and 5,8,8-Trimethyl-bicyclo(3.2.1)oct-3-en-2-one (XLIV, XLVI).[112]

A solution of a mixture of the methyl ethers (10 g, 0.052 mole) in anhydrous ether (50 ml) was added dropwise with stirring to a suspension of lithium aluminum hydride (1.5 g, 0.04 mole) in anhydrous ether (125 ml). The solution was stirred at reflux for two hours, cooled in an ice bath, and a mixture of ice (22 g) and water (8 ml) added carefully with stirring. Concentrated sulphuric acid (30 ml) was added very slowly (2-2.5 hr), while maintaining the temperature of the solution below 15°. After stirring at room temperature for twelve hours, the mixture was extracted with ether (three times), and the combined extracts washed successively with aqueous 10% sodium bicarbonate solution and water, dried, filered and concentrated to provide a yellow waxy solid (7.0 g, 85%) with the characteristic odour of camphor.

Addition of benzene induced crystallization.

I.r. (CCl_4): 1710 (sh), 1680 cm^{-1}.

N.m.r. (CCl_4): δ0.90, 0.92, 1.00 and 1.23 (4 s, 9 H), 1.3-2.7 (complex, 5 H), 5.77 (d, J=9 cps, 1 H), 5.80 (d, J=9 cps, 1 H), 6.67 (d, 1 H), 7.00 (d of d, 1 H, C_4 vinyl split by C_3 vinyl, J=9 cps, and split by C_5 proton, J=7 cps) ppm.

Hydrogenation of 1,8,8- and 5,8,8-Trimethylbicyclo-(3.2.1)oct-3-en-2-one (XLIV, XLVI): Formation of 1,8,8-Trimethylbicyclo(3.2.1)octan-2-one (Homocamphor) (IX) and 5,8,8-Trimethylbicyclo(3.2.1)octan-2-one (Homoepi-camphor) (XLVII).

A solution of the unsaturated ketones (XLIV and XLVI) (5.0 g, 0.031 mole) in 95% ethanol (60 ml), containing a catalytic amount of platinum dioxide (0.104 g) and pyridine (0.6 ml) was hydrogenated at atmospheric pressure and room temperature. The solution was filtered through Celite and concentrated to afford a pale yellow oil (4.9 g, 97%). G.l.c. analysis (Column A, 130°) indicated the two ketones were present in a 1:1 ratio.

I.r. (CCl_4): 1708 cm^{-1}.

N.m.r. (CCl_4): δ0.87, 0.95 and 0.97 (3 s, 9 H), 1.2-2.6 (complex, 9 H) ppm.

Preparation of the Semicarbazone of Homoepicamphor (XLVII): Isolation of Homocamphor (IX).

To a 1:1 mixture of homo- and homoepicamphor (1.01 g, 0.006 mole) was added aqueous semicarbazide hydrochloride solution (1.5 ml, 0.5 molar equivalent) and enough methanol (~3 ml) to produce a clear solution. After the addition of pyridine (0.38 ml, 0.005 mole), the mixture was heated gently on a steam bath for ten minutes, cooled and the semicarbazone filtered, washed successively with cold water and benzene, dried in a vacuum dessicator to yield a crystalline solid, m.p. 207-211°C.

I.r. (Nujol): 3415 (sh, NH), 3300-3100 (br, NH), 1715 (C=O, ket.), 1690 (C=O, amide) cm^{-1}.

N.m.r. (d_6-DMSO): δ0.72 (s, 3 H), 0.83 (s, 6 H), 1.0-2.4 (complex), 6:0 (br, 2 H), 8.8 (br, 1 H) ppm.

The filtrate was acidified with 6N hydrochloric acid, the layers separated, and the aqueous layer extracted with diethyl ether (twice). The combined organic extracts were washed with water until the washings were neutral, dried, filtered and concentrated to afford a colourless oil which crystallized on the addition of a few drops of benzene. Purification of homocamphor was achieved by preparative g.l.c. (Column A, 187°) or by

thin layer chromatography on silica gel, eluting with 10% ether-petroleum ether. The melting point of homocamphor was 178-179°C (sealed tube) (lit.[111] m.p. 187-190°C).

I.r. (CCl_4): 1706 cm^{-1}.

N.m.r. (CCl_4): δ0.79, 0.85 and 0.88 (3 s, 9 H), 1.1-2.4 (complex, 9 H) ppm.

Hydrolysis of Methyl Ethers (XLI, XLII): Formation of 1,8,8-Trimethylbicyclo(3.2.1)octan-2,4-dione (XLIIIa).

An ethereal solution of the methyl ethers (3.2 g, 0.017 mole) obtained from ring expansion of camphorquinone was stirred at room temperature with aqueous 15% hydrochloric acid (20 ml) for three days. After separation of the layers and extraction of the aqueous layer with diethyl ether (three times), the combined ethereal extracts were extracted with aqueous 10% sodium hydroxide (twice) and the alkaline layers acidified with concentrated hydrochloric acid (Congo Red). The resulting solid was filtered, washed with water until the washings were neutral and dried in a vacuum dessicator. After recrystallization from benzene, the dione was obtained (1.8 g, 62%), m.p. 220-222°C (sealed tube) (lit.[111] m.p. 222-224°C). The mass spectrum displayed a molecular ion peak at m/e 180.

I.r. ($CHCL_3$): 3550-3100 (br, weak, OH), 1730, 1710 (C=O) cm^{-1}. N.m.r. ($CDCl_3$): 60.80, 1.03 and 1.08 (3 s, 9 H), 1.6-2.8 (complex), 3.18 (s, 1 H), 3.37 (s, 1 H) ppm.

Preparation of the Semicarbazone of 1,8,8-Trimethylbicyclo(3.2.1)octan-2,4-dione (XLIIIc).

To a sample of the dione (XLIIIa) (1.8 g, 0.010 mole) was added aqueous semicarbazide hydrochloride solution (5 ml, 0.010 mole) and enough methanol to produce a clear solution. After the addition of pyridine (~1 ml), the reaction was heated gently on a steam bath for ten minutes, and a few drops of water added to induce precipitation. The solid was filtered and washed with benzene. Recrystallization from 95% ethanol provided the semicarbazone (XLIIIc) as fine needles (1.8 g, 76%), m.p. 230-231°C. A molecular ion peak at m/e 237 in the mass spectrum indicated the product was the monosemicarbazone.

Anal Calc. for $C_{12}H_{19}N_3O_2$: C, 60.73; H, 8.07; N, 17.71.

Found: C, 60.74; H, 8.20; N, 17.59.

I.r. (Nujol): 1705 (C=O, ket.), 1690 (C=O, amide) cm^{-1}.

Potassium t-Butoxide Reduction of the Semicarbazone (XLIIIc): Formation of 1,8,8-Trimethylbicyclo(3.2.1)octan-2-one (Homocamphor) (IX).

A solution of the semicarbazone (0.080 g, 0.0034 mole) in 1:1 m-xylene and 1-pentanol (6 ml) was stirred at reflux for one and one half hours with careful monitoring of the reaction by g.l.c. Water was added carefully, the layers separated and the organic layer washed with a small amount of dilute acetic acid, followed by aqueous 5% sodium bicarbonate solution and water until the washings were neutral. The organic solvents were removed by azeotroping with water under reduced pressure to provide an oil. G.l.c. analysis indicated one component. The mass spectrum displayed peaks at m/e 42 (base peak), 43, 55 (base peak), 57, 69, 71 and 164. I.r. (CCl_4): 1675, 1700 (sh) cm^{-1}.

Preparation of 3,3-d_2-Bicyclooctanones (XVII, XXV, IX).[92]

A solution of the ketone (0.050 g, 0.0004 mole) in dioxane (0.16 ml) was treated with a solution of sodium hydroxide (0.5 g, 0.013 mole) in deuterium oxide (0.670 ml) and the reaction stirred at 45° for six days. The reaction was followed by the disappear-

ance of the absorption due to the α-protons in the n.m.r spectrum. The mixture was extracted with ether, the organic phase washed with deuterium oxide until the washings were neutral, dried, filtered and concentrated to yield an oil. The products were obtained in yields ranging from 75 to 99%. The mass spectra of the deuterated compounds indicated isotopic purities of 71-95%.

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